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Reduction in coronary mortality in England between 2000 and 2007: the contribution of medication and dietary change in primary prevention

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Key words: Coronary heart disease mortality, inequalities, blood pressure, cholesterol, Rose's approach, primary prevention.

Abstract

Objective

To analyse the falls in coronary heart disease (CHD) mortality in England between 2000-2007 and quantify the relative contributions from preventive medications and from population-wide changes in blood pressure (BP) and cholesterol levels, particularly exploring socioeconomic inequalities.

Design

A modelling study.

Setting

Sources of data included controlled trials and meta-analyses, national surveys and official statistics.

Participants

Population aged 35+ in England in 2000-2007.

Main outcome measures

Number of deaths prevented or postponed (DPPs) in 2007 by socioeconomic status. We used IMPACT$_{SEC}$ model which applies the relative risk reduction quantified in previous randomised controlled trials and meta-analyses to partition the mortality reduction among specific treatments and risk factor changes.

Results

Between 2000-2007, approximately 22,500 DPPs were attributable to reductions in BP and cholesterol in the English population.

The substantial decline in BP was responsible for approximately 13,000 DPPs. Approximately 1,800 DPPs came from medications and some 11,200 DPPs from population-wide changes.

Reduction in population BP resulted in approximately 2,400 DPPs in the most deprived quintile compared with 1,900 DPPs in the most affluent.

Reduction in cholesterol resulted in approximately 7,400 DPPs; approximately 5,300 DPPs were attributable to statin use and approximately 2,100 DPPs to population-wide changes.

Statins prevented more deaths in the most affluent quintile (1,100 DPPs) compared with the most deprived (800 DPP). Conversely, population-wide changes in cholesterol prevented threefold more deaths in the most deprived quintile (700 DPPs) compared with the most affluent (230 DPPs).

Conclusions

Population-wide secular changes in blood pressure and cholesterol levels helped to substantially reduce CHD mortality and the associated socioeconomic disparities. Mortality reductions were

greatest in the most deprived quintiles, mainly reflecting their bigger initial burden of disease. Statins for high-risk individuals also made an important contribution but maintained socioeconomic inequalities. Future CHD prevention strategies should prioritise healthy diet policies ahead of medications.

Strengths

- This is the first IMPACT model to quantify the contributions of population risk factors and primary prevention treatments to recent changes in CHD mortality rates by socioeconomic quintiles.
- The datasets used for the model are representative of the English population and used deprivation scores for area of residence as an acceptable proxy indicator for socioeconomic status.
- Unlike, the previous IMPACT$_{SEC}$ models (Bajekal, Scholes (1) and Scholes, Bajekal (2)), our study stratifies the analysis and results by gender. This allowed us to gain valuable new insights, for example changes in SBP and cholesterol population levels for women led to the highest number of DPPs for all quintiles. More surprisingly, the change in uptake levels for women in the least deprived quintile was almost as effective as the population-wide changes in SBP and cholesterol for both sexes. This all suggests that any attempt to tackle the socioeconomic inequalities in CHD mortality should explicitly consider these gender differences.

Limitations

- The area-level categorisation may not be representative of individual circumstances. A small number of very deprived people in one postcode might drive down the average score, and vice versa.
- Observed differences in CHD mortality might reflect not material deprivation but other confounding factors such as alcohol consumption, obesity or ethnicity. However, there is increasing evidence to support the use of IMD quintiles as a reasonable proxy of SES (3).
- We assumed that reductions in the risk factors will have equal benefit across socioeconomic groups. However, the benefits of a unit fall in blood pressure or cholesterol may be higher in more affluent groups (effect modification) (1). This may partly explain the faster rates of CHD mortality decline in the most affluent quintiles. Likewise, we assumed that the relative risk reduction due to treatments remained constant from 2000 to 2007.
- We simply subtracted the mortality gains from increasing uptake levels of statins from the overall gains due to reductions in total cholesterol to estimate the impact of population-wide reduction in total cholesterol due to non-pharmacological change only. This adjustment might overestimate medication benefit.
- Finally, our model was not able to explain around 14% of the total CHD mortality fall between 2000 and 2007.

Introduction

The UK has experienced a remarkable 60% reduction in coronary heart disease (CHD) mortality since the 1970s. However CHD remains the leading cause of premature death (4).

Approximately one third of this initial CHD mortality reduction was attributable to treatments, and two thirds to reductions in major risk factors. The biggest contributions came from a large decline in smoking prevalence since the 1960s, and more recent reductions in blood pressure and cholesterol (1, 5).

The CHD mortality declines have demonstrated a changing relationship with socio-economic status (SES) (6-8). CHD initially demonstrated a positive relationship with SES (i.e. with affluence) (9). However, this has now reversed in more recent studies in the UK, US, New Zealand, Australia, and Scandinavia. In the Whitehall study, civil servants were classified into four ascending grades of employment reflecting salary status, education and work responsibility. After a 25-year follow up, those in the lowest grade had 1.5 times greater risk of CHD death than those in the highest grade (10). Also, the FINMONICA MI Register (a longitudinal Finnish study) revealed even greater disparities in CHD mortality and morbidity rates between the most and least affluent groups (11); the Scottish Heart Health Study also reported a positive association with CHD and deprivation. Furthermore, recent UK (12) analyses reported a faster rate of decline in annual CHD mortality in the most affluent groups compared with the most deprived.

Risk factors have also demonstrated strong socioeconomic patterning. Substantial positive associations between lower SES and higher smoking prevalence and higher blood pressure levels have been reported in several studies (13-15). However, for cholesterol, the evidence has been less dramatic, with a higher intake of saturated fats among the more deprived populations reported in most studies (16-18), but not all (19-21). Socioeconomic differences in both risk factors may thus explain some of the CHD mortality gradients. Thus, any attempt to reduce the CHD burden and tackle the associated socioeconomic inequalities should explicitly consider these major risk factors (22).

Primary prevention medications to lower blood pressure and cholesterol have therefore been standard UK health policy for almost two decades. However, while their quantitative benefits to whole populations are accepted, their potential contributions to reduce inequalities are less clear (7,9,21,28,29,35,36). The aim of this study was therefore to analyse the recent falls in CHD mortality and quantify the relative contributions from preventive medications and from population-wide changes in blood pressure and cholesterol levels, particularly exploring the potential effects on socioeconomic inequalities.

Methods

We used an extended version of the well-known IMPACT model to estimate the contributions of population-level risk factor changes and changes in treatment uptake on the CHD mortality decline in England between 2000 and 2007 for adults aged 25 and over, for two major risk factors, blood pressure and cholesterol (12).

The IMPACT model applies the relative risk reduction quantified in previous randomised controlled trials (RCT) and meta-analyses to estimate the mortality reduction attributable to a) temporal change in risk factor prevalence and b) net change over the period in the uptake of specific treatments in patients with each specific form of CHD. This previously validated deterministic cell-based model has been described in detail elsewhere (23, 24).

The extended version IMPACT$_{SEC}$ model (1) includes all the major CHD risk factors: smoking, systolic blood pressure (SBP), total cholesterol, body mass index (BMI), diabetes, physical inactivity and fruit and vegetable consumption. It also includes 45 medical and surgical treatments employed in nine different patient groups. Additionally, the model allows exploring the variation in CHD mortality trends due to socioeconomic circumstances. Model inputs and outputs are stratified by the Index of Multiple Deprivation (IMD) quintiles as a proxy indicator of SES (16).

Our primary outcome measure was the total number of deaths prevented or postponed (DPPs) for each deprivation quintile that can be attributed to either population-level risk factor changes in SBP and cholesterol or changes in the uptake of anti-hypertensive and dyslipidaemia treatments. DPPs are defined as the difference between the number of expected deaths on 2007 (had age, sex, and SES quintile-specific CHD mortality rates in 2000 remained unchanged) and the observed figures.

The starting point for the model was to calculate the expected number of CHD deaths in 2007 by multiplying the age-sex-IMD quintile specific mortality rates from CHD in 2000 by the population counts for 2007 in that age-sex-IMD quintile stratum. Summing over all strata then yielded the expected number of deaths in 2007 had mortality rates remained unchanged. The difference between the number of expected and observed deaths from CHD represented the mortality fall or the total DPPs in 2007 relative to 2000. Sources for the population counts, CHD mortality rates and observed numbers of deaths are shown in Table A of the Technical Appendix.

To calculate the net benefit of statins and anti-hypertensive treatment in 2007, we subtracted the expected number of DPPs if the uptake rates in 2000 remained constant from the estimated number DPPs using the 2007 uptake rates. The expected number of DPPs from statins and anti-hypertensive treatment, if the uptake rates in 2000 remained constant, were calculated by multiplying the 2000 age-sex-IMD quintile specific treatments uptake levels by the population counts for 2000 in that age-sex-IMD quintile stratum, the one-year case fatality rate and the relative reduction in the case fatality rate due to the administered treatment. We did the same for the expected number if DPPs in 2007 but now using 2007 age-sex-IMD quintile specific treatments uptake levels. The uptake levels for anti-hypertensives and statins were defined as the prevalence of never having had angina or heart attack and

currently taking medication specifically prescribed to treat high blood pressure or lipid lowering treatment respectively. Sources for treatment uptake, estimates of treatment efficacy (relative risk reductions) and age-sex specific case fatality rates for each patient group are presented in Table A of the Technical Appendix.

The second part of the $IMPACT_{SEC}$ model estimated the number of DPPs related to changes in SBP and cholesterol levels in the population. To calculate DPPs from changes in risk factors, we used the regression approach, where the number of CHD deaths in 2000 were multiplied by the absolute change in risk factor level (absolute difference in the risk factors levels between 2000 and 2007 risk factor levels), and by a regression coefficient ('beta') quantifying the estimated relative change in CHD mortality that would result from a one-unit change in risk factor level. Sources for trends in the risk factors mean levels and beta coefficients are presented in Table A of the Technical Appendix.

Recent reductions in CHD mortality have been the result of simultaneous change in multiple risk factors. Hence, part of the effect of one risk factor may be mediated through another. In this regard, we used a cumulative risk reduction adjustment factor (AF) to adjust down the DPPs attributed to multiple risk factors acting additively or separately, more details can be found in the Appendix 1.1.

Also we considered that some overlap between pharmacological and non-pharmacological contributions to risk factor DPPs might occur. Therefore, to estimate the impact of population-wide reduction in total cholesterol due to non-pharmacological change only, we subtracted the estimated effect of cholesterol-lowering treatments uptakes levels change from the overall number of DPPs due to change in mean total cholesterol. A similar procedure was carried out for SBP and anti-hypertension treatments.

Finally, we implemented sensitivity analysis using the EXCEL add-in Ersatz software which allows Monte Carlo simulation. This allows us to calculate 95% uncertainty intervals (95% UI) for all outputs, based on 5000 draws from specified probabilistic distributions for the model input variables. The parameter distributions used for the input variables to the DPP calculations are shown in Appendix 1.3

Results

Systolic blood pressure (SBP) and cholesterol population levels

Figures 1 depicts the trends in population systolic blood pressure and cholesterol levels between 2000 and 2007, stratified by IMD quintiles and sex. Systolic blood pressure fell substantially between 2000 and 2007, by an average of 5.4 mmHg in women and 2.5 mmHg in men. Total cholesterol also fell (by approximately 0.20mmol/l), but equally in men and women.

There was no evidence of a social gradient, since the population factors levels were similar across IMD quintiles with no statistically significant difference between them.

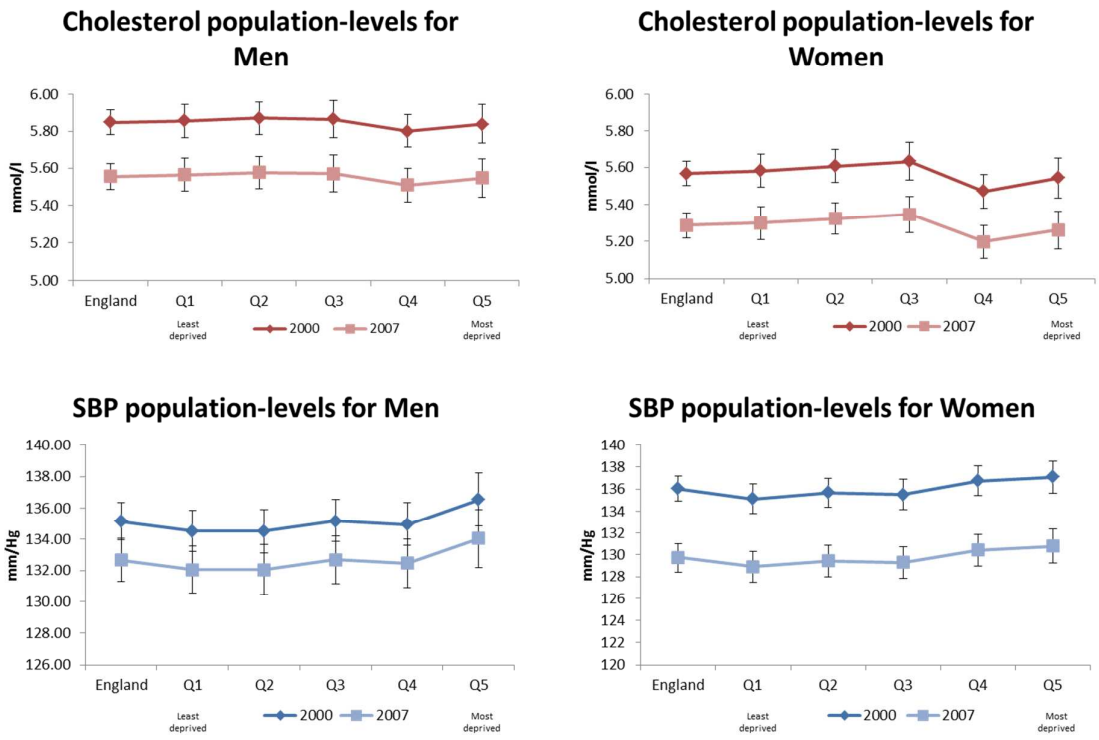


Figure 1: Mean values of SBP and cholesterol between 2000 and 2007 for England and stratified by deprivation quintiles and sex (95% uncertainty intervals). Uncertainty intervals were calculated via Monte Carlo simulation.

Antihypertensive and statin treatment uptakes

Figure 2 depicts treatments uptakes between 2000 and 2007: there was a substantial increase in both treatment uptakes, especially statins. Uptakes levels of anti-hypertensive treatments and statins were remarkably equitable across quintiles for men and women, with no statistically significant differences between them.

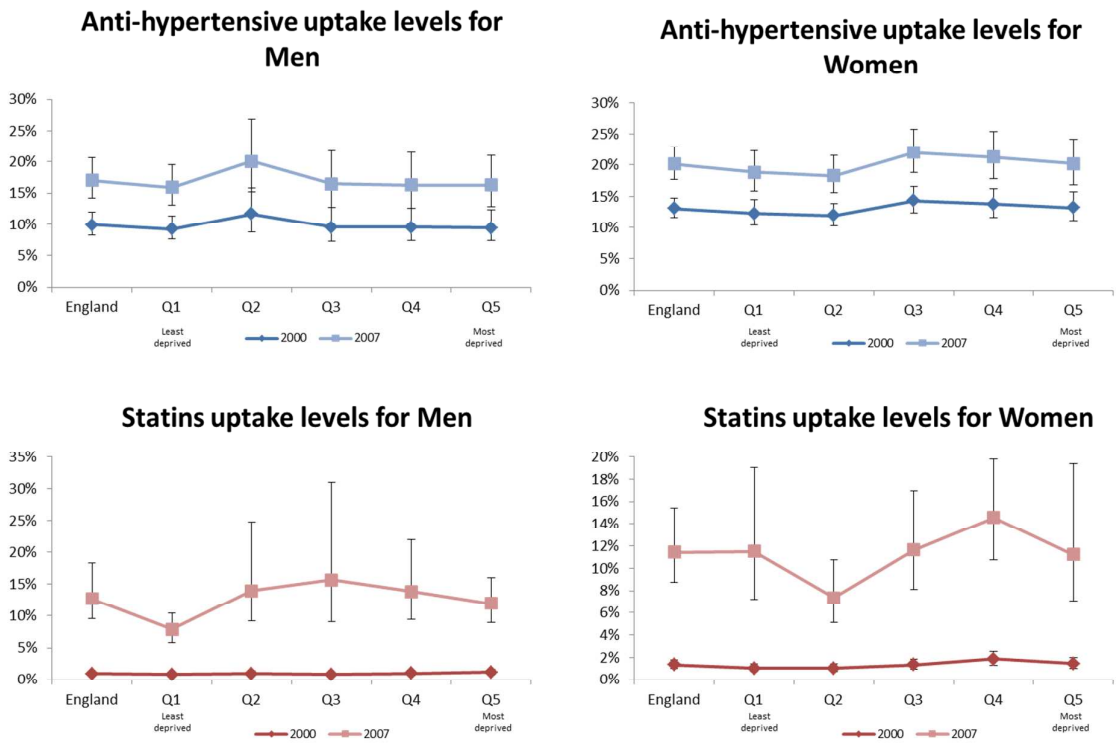


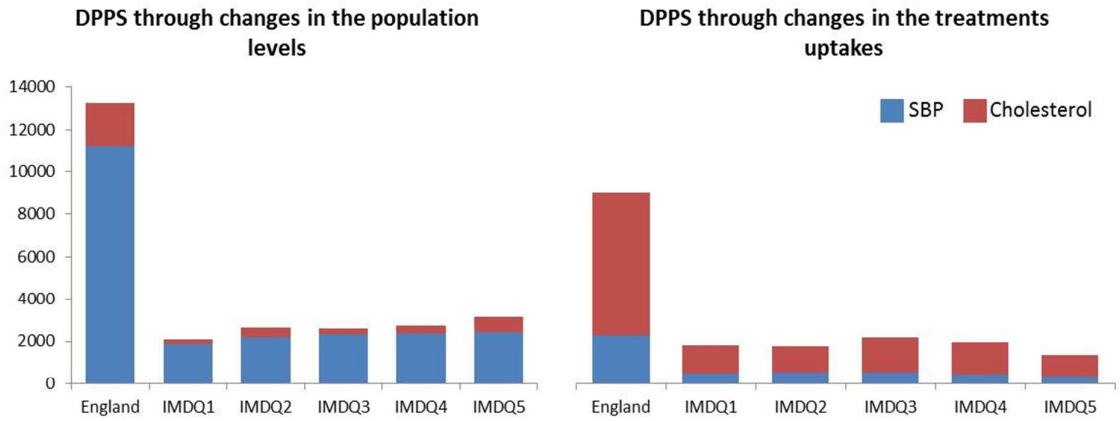
Figure 2: Uptake levels and proportion change in treatment uptake between 2000 and 2007 for England stratified by deprivation quintiles (95% Uncertainty intervals). Uptake levels of anti-hypertensive medication and statins were estimated using the methodology described in (2). Uncertainty intervals were calculated via Monte Carlo simulation.

Deaths prevented or postponed

There were approximately 38,000 fewer CHD deaths in 2007 than if 2000 mortality rates had persisted and been applied to 2007 population estimates for England. Our model was able to explain 32,800 (86.3%) of these fewer deaths (see Table 3). Approximately 7,100 (95% UI, 3500 – 14,200) fewer deaths (22% of the total mortality reduction) were attributed to changes in the uptake levels of treatments for high blood pressure and raised cholesterol. Approximately 13,300 (8,500– 17,400) DPPs (41% of the mortality reduction) were attributed to population-wide changes in blood pressure and cholesterol in asymptomatic individuals after subtracting the estimated effect of changes in treatment uptakes. The remaining 37% of the deaths prevented or postponed in our model were attributed to other risk factors and treatments.

Deaths prevented or postponed (DPP)						
	England	IMD quintile 1 Affluent	IMD quintile 2	IMD quintile 3	IMD quintile 4	IMD quintile 5 Deprived
Mean	32770	5775	6745	7015	6870	6370
95% LL	25985	4430	5320	5420	5400	5100
95% UL	41550	7705	8515	9360	8765	7830

Table 1: CHD deaths prevented or postponed between 2000 and 2007 in England, stratified by deprivation quintiles, and rounded to the nearest 5.



DPPs	England	IMD 1	IMD 2	IMD 3	IMD 4	IMD 5
Total	13253	2093	2666	2608	2742	3143
SBP	11162	1861	2168	2321	2391	2421
Cholesterol	2091	232	498	287	351	722

DPPs	England	IMD 1	IMD 2	IMD 3	IMD 4	IMD 5
Total	7098	1411	1386	1713	1539	1049
SBP	1798	357	411	408	345	277
Cholesterol	5300	1054	975	1305	1194	772

Figures 3a and 3b: Number of deaths prevented or postponed (DPPs) between 2000 and 2007 in England attributable to changes in the population in SBP and cholesterol (Fig 3a), changes in uptakes levels for anti-hypertensive treatments and statins (Fig 3b); stratified by deprivation quintiles

Figures 3a and 3b show the number of deaths prevented or postponed from changes in the population mean levels of SBP and Cholesterol (Figure 3a, left panel) and from changes in the treatment uptakes levels (Figure 3b, right panel). We can highlight some key aspects:

1) Population changes in SBP and cholesterol resulted in more DPPs than treatment uptake levels changes of anti-hypertensives and statins. 2) Most of the mortality reduction through population changes reflected changes in SBP rather than in cholesterol. c) By contrast, most of the effect of treatment uptake levels changes was though increments in the uptake levels in statin use rather than antihypertensive use. 3) Substantial numbers of DPPs were observed in all social class groups. 4) The absolute effect of population changes on DPPs was been bigger among the most deprived people. 5)

By contrast, the number of DPPs attributable to was remarkably equitable across SES groups. However, statin uptakes apparently postponed or prevented slightly more deaths in the most affluent quintile than in the most deprived quintile (Fig 3b).

Systolic blood pressure

Overall, SBP falls between 2000 and 2007 prevented or postponed approximately 13,000 (8,100 - 17,500) deaths. Approximately 1,800 (700-3,900) of those were attributable to anti-hypertension treatments and some 11,200 DPPs (6,500-15,100), over six fold more, were attributable to population-wide SBP changes. Substantially more DPPs through population-wide changes occurred in the most deprived 2,400 (1,600-3,100) compared with the most affluent quintiles: 1,800 (1,000-2,600). Thus population-wide changes apparently helped to reduce inequalities. Conversely, changes in treatment uptake levels demonstrated the opposite effect, since more deaths were prevented in the most affluent quintile compared to the most deprived. However both SES differences were not statistically significant. Detailed outputs with uncertainty intervals can be found in the Technical Appendix.

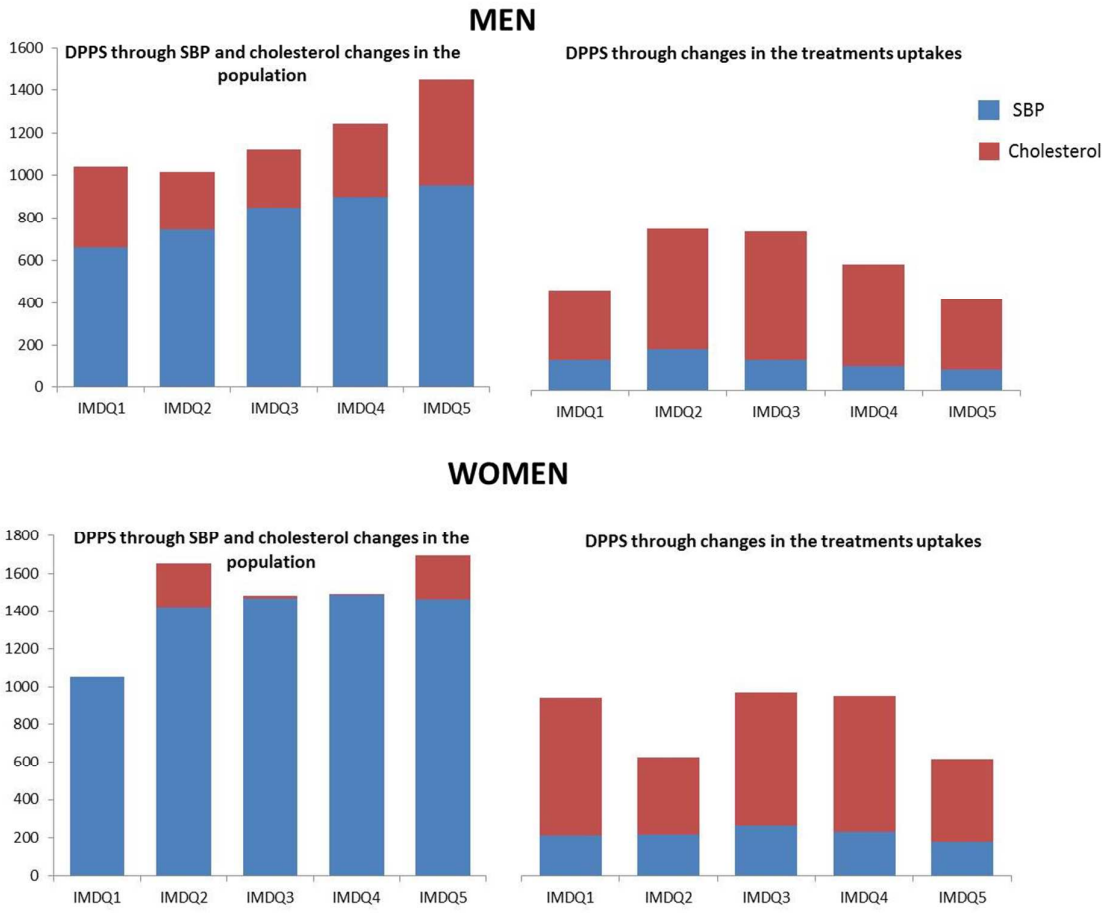
Cholesterol

Overall, cholesterol falls between 2000 and 2007 resulted in approximately 7,400 (3,900-14,500) fewer deaths (Table 6). This total comprised some 5,300 (2,100-12,300) fewer deaths attributable to statin medications and approximately 2,100 (1,000-3,200) fewer deaths attributable to population-wide falls in cholesterol. Statin medications prevented some 1,100 (400-2,700) deaths in the most affluent quintile compared to approximately 800 (300-1,900) DPPs in the most deprived quintile. Conversely, population changes in cholesterol resulted in approximately 700 (500-1,000) DPPs in the most deprived quintile and some 200 (40-400) DPPs in the most affluent quintile. However, there was no a clear SES gradient. (The Technical Appendix provides detailed outputs with uncertainty intervals).

Gender differences

Figures 4 shows the number of deaths prevented or postponed in men and women, from changes in the population mean levels of SBP and Cholesterol (Figure 4a, left panels) and from changes in the treatment uptakes levels (Figure 4b, right panels). For men, although most of the mortality reduction came from population levels reduction in SBP, cholesterol reductions have a considerable larger effect in reducing mortality in men than in women. By contrast, the number of DPPs due to changes in treatments in men appeared remarkably equitable across SES groups.

For women, the impressive reduction in SBP mean level between 2000 and 2007, contributed the most to the total mortality reduction and in all quintiles, whereas population level reductions of cholesterol had a smaller benefit. Moreover, the joint benefit of increasing treatment uptakes (antihypertensive and statins) in women appeared to have a greater impact than in men: for example, in the most affluent quintile (IMDQ1) the reduction in DPPs due to the favourable change in uptakes for women was almost as effective as the population-wide changes in both sexes. More detailed outputs split by gender can be found in the Technical Appendix.



Figures 4and 4b: Number of DPPs from changes in the population in SBP and cholesterol, changes in uptakes levels for anti-hypertension and dyslipidaemia between 2000 and 2007 in England, stratified by deprivation quintiles

Discussion

Coronary heart disease mortality in England fell by a remarkable 34% between 2000 and 2007. This represents an impressive 38,000 fewer deaths from CHD in 2007 than if the 2000 mortality rates had persisted. Reductions in major cardiovascular risk factors of blood pressure and cholesterol explained almost two thirds of this large mortality fall.

Blood pressure trends

Declines in the population blood pressure level made the largest contribution to the overall fall in CHD mortality. In contrast, anti-hypertension treatments produced only modest benefits (25). Firstly, because the baseline CHD event rate was low in asymptomatic individuals (≤ 1% per year) yielding only a small reduction of the attributable risk. Secondly, efficacy is low with substantial residual risk and thirdly blood pressure control is still poor (adherence levels to medication are around 60%) (9), leading to a substantial residual risk (23, 26).

Cholesterol trends

Population-wide falls in cholesterol levels averted more deaths in the most deprived quintiles, reflecting similar absolute falls but much higher baseline mortality rates. Statins made an even greater contribution to the overall mortality fall: two fold greater than the change in population cholesterol (16% versus 6%), and with equitable benefits across all five SES groups.

Comparisons with other studies

Our results are consistent with previous analyses in the UK and around the world, supporting the importance of this study beyond England. Using the IMPACT model to examine contributions to the overall reductions in CHD mortality in England and Wales population between 1981 and 2000, Unal, Critchley (5) reported a higher contribution from blood pressure changes (compared to cholesterol). Some 76% of this contribution was attributable to population-wide changes rather than anti-hypertensive medications. IMPACT analyses carried out in the US and Irish populations between 1980-2000 and 1985-2000 likewise observed substantially greater benefits attributable to secular changes in risk factors rather than treatments (24, 27).

The analysis by De Wilde et al suggested that reported blood pressure treatments were responsible only for the 25% of 5mmHg reduction in SBP during the period 1994-2009 for England. DeWilde, Carey (28)

Emberson et al Emberson, Whincup (29) applied a very different methodology using evidence from randomised control trials and cohort studies to analyse the effectiveness of population-wide changes in risk factor levels against the high risk individual approach. Their findings were entirely consistent

with ours. They concluded that a mere 10% reduction in population-wide blood pressure and cholesterol levels might achieve a 45% reduction in cardiac events in the long term. However, approximately 26% of the UK population in high risk would need medications to achieve a 34% reduction in cardiac events. The US CHD policy model likewise reported that population-wide reductions of salt intake (3 g per day) might prevent between 44,000 and 90,000 deaths (30).

Strengths & limitations

This is the first IMPACT model to quantify the contributions of population risk factors and primary prevention treatments to recent changes in CHD mortality rates by socioeconomic quintiles.

The datasets used for the model are representative of the English population and used deprivation scores for area of residence as an acceptable proxy indicator for socioeconomic status. This allowed a sufficient sample size to quantify the effect of risk factor modification through changes in population-wide risk factor levels and treatment uptake.

Unlike, the previous IMPACT$_{SEC}$ models (Bajekal, Scholes (1) and Scholes, Bajekal (2)), our study stratifies the analysis and results by gender. This allowed us to gain valuable new insights, for example changes in SBP and cholesterol population levels for women led to the highest number of DPPs for all quintiles. More surprisingly, the change in uptake levels for women in the least deprived quintile was almost as effective as the population-wide changes in SBP and cholesterol for both sexes. This all suggests that any attempt to tackle the socioeconomic inequalities in CHD mortality should explicitly consider these gender differences.

However, our study limitations should also be acknowledged. Firstly, the area-level categorisation may not be representative of individual circumstances. A small number of very deprived people in one postcode might drive down the average score, and vice versa. Furthermore, observed differences in CHD mortality might reflect not material deprivation but other confounding factors such as alcohol consumption, obesity or ethnicity. However, there is increasing evidence to support the use of IMD quintiles as a reasonable proxy of SES (3).

Thirdly, we assumed that reductions in the risk factors will have equal benefit across socioeconomic groups. However, the benefits of a unit fall in blood pressure or cholesterol may be higher in more affluent groups (effect modification) (1). This may partly explain the faster rates of CHD mortality decline in the most affluent quintiles. Likewise, we assumed that the relative risk reduction due to treatments remained constant from 2000 to 2007.

Fourthly, we simply subtracted the mortality gains from increasing uptake levels of statins from the overall gains due to reductions in total cholesterol to estimate the impact of population-wide reduction in total cholesterol due to non-pharmacological change only. This adjustment might overestimate medication benefit.

Finally, our model was not able to explain around 14% of the total CHD mortality fall between 2000 and 2007. One possible contributor might be the exclusion of other "upstream" cardiovascular risk factors, which might affect SES groups differentially, for example, psychosocial stress (31).

Implications for public health and clinical care

This study shows that population-wide secular falls in blood pressure and cholesterol have substantially helped to decrease CHD mortality and reduce the associated socioeconomic disparities. Furthermore, as we discussed earlier, there is an increasing body of evidence to support the use of population-wide approaches to reduce CHD risk factors. Mackenbach, Lingsma (32) recently evaluated 22 successful preventive interventions in the Netherlands. Approximately 75% of the health gains during the period 1970-2010 were achieved by a population approach and just 25% by a high risk individual approach.

In the UK, the population-wide fall in blood pressure is consistent with the recent successful implementation of policies to reduce salt intake. Similar trends have been reported in other developed countries (23, 26). There are also several international examples where policy interventions have proven to be effective at achieving significant reductions in saturated fats, trans-fats and calories in processed foods and takeaway meals (30, 33-35). However policies to reduce saturated fats and trans-fats have thus far been neglected in the UK (36).

Conversely, targeting high-risk individuals with medication appears less effective and may also widen socioeconomic inequalities in CHD mortality (37,38). Any intervention that requires people to mobilise their own resources (material and psychological) will understandably favour those who have greater resources (37) and thus widen social inequalities. Thus, those with the poorest health will benefit the least from such interventions (38).

However, there is no simple choice between either population-based or high risk strategies to reduce CHD mortality. The approaches are complementary in delivering the greatest public health benefit (39, 40). It is, however, clear that individual-based treatment strategies can afford only modest reductions in mortality compared with addressing risk factors population wide.

Severely limited health care budgets are now forcing planning systems to consider how best to allocate future resources. Our results strengthen the case for greater emphasis on preventive approaches, particularly population based policies to reduce blood pressure and cholesterol. Such strategies might be more powerful, rapid, cost-effective, and equitable than additional preventive medications (36).

Author contributions

MGC drafted the manuscript, analysed the results and conducted the uncertainty analysis in collaboration with S Capewell, M O'Flaherty and R. Ahmed. R. Ahmed conducted the initial literature review and initial set up of the model in collaboration with S Capewell. N Hawkins, S Scholes, E Wilkinson, J Lucy contributed to the interpretation of the results and to the drafting and finalisation of the manuscript

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Details of funding

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Data sharing statement

Data, $IMPACT_{SEC}$ spreadsheet and detailed results are available upon request by emailing Maria Guzman-Castillo.

Role of sponsor

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Transparency declaration

The lead author Maria Guzman Castillo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been reported.

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STROBE statement checklist of items that should be included in reports of observational studies

Reduction in coronary mortality in England between 2000 and 2007: the contribution of medication and dietary change in primary prevention

Maria Guzman Castillo et al.

	Item No	Recommendation	
		Title and abstract	
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	No
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract attached (page 5)
		Introduction	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background & rationale explained page 5
Objectives	3	State specific objectives, including any pre-specified hypotheses	Specific objective stated in page 5
		Methods	
Study design	4	Present key elements of study design early in the paper	Key elements presented Pages 6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Data collection specified and fully detailed in the technical appendix and pages 6-7
Participants	6	(*a*) *Cohort study*? Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*? Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	NA
		Cross sectional study? Give the eligibility criteria, and the sources and methods of selection of participants	**Cross sectional study.** eligibility criteria, sources and methods of selection of cases clearly specified in the technical appendix and methods (page 6-7)
		(*b*) *Cohort study*? For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*? For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers.	Outcomes, exposures, predictors, potential confounders, and effect modifiers clearly described. Pag 6-

	Item No	Recommendation	
		Give diagnostic criteria, if applicable	Pages 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Diagnostic criteria based on ICD codes.
Bias	9	Describe any efforts to address potential sources of bias	Age adjustment and stratification by socio-economic circumstances detailed. Pages 6-7
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods described in detail Pages 6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical methods described in detail Pages 6-7 and Technical appendix
		(*b*) Describe any methods used to examine subgroups and interactions	Subgroup analyses detailed Pages 6-7 and Technical appendix
		(*c*) Explain how missing data were addressed	Details on how missing data were addressed are included. Page 15 Technical appendix
		(*d*) *Cohort study*? If applicable, explain how loss to follow-up was addressed *Case-control study*? If applicable, explain how matching of cases and controls was addressed *Cross sectional study*?If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	Sensitivity analysis implemented and described Pages 6-7 and Technical appendix
		Results	
Participants	13*	(*a*) Report numbers of individuals at each stage of study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Reported Pages 8-11, 14-16 and technical appendix
		(*b*) Give reasons for non-participation at each stage	NA
		(*c*) Consider use of a flow diagram	NA
Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Details provided Reported Pages 8-11, 14-16 and technical appendix
		(*b*) Indicate number of participants	NA

	Item No	Recommendation	
		with missing data for each variable of interest	
		(*c*) *Cohort study*? Summarise follow-up time (eg average and total amount)	NA
		Cohort study? Report numbers of outcome events or summary measures over time	NA
Outcome data	15*	*Case-control study?* Report numbers in each exposure category, or summary measures of exposure	NA
		Cross sectional study? Report numbers of outcome events or summary measures	Events detailed Reported Pages 8-11, 14-16
Main results	16	(*a*) Report the numbers of individuals at each stage of the study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Numbers detailed
		(*b*) Give reasons for non-participation at each stage	NA
		(*c*) Consider use of a flow diagram	NA
Other analyses	17	Report other analyses done? eg analyses of subgroups and interactions, and sensitivity analyses	Sub-group analyses and comparisons detailed Sensitivity analysis implemented and described Reported Pages 14-16 and technical appendix
		Discussion	
Key results	18	Summarise key results with reference to study objectives	Key results summarised. Reflect objectives.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations and potential biases discussed in detail Page 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Cautious throughout. Pages 8-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Generalisability briefly discussed. Pages 8-11, 14-16
		Other information	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present	Funding sources detailed Page 2

Item No	Recommendation
	article is based

Technical Appendix

1 Cumulative risk-reduction: adjusting deaths prevented or postponed (DPPs) to calculate combined benefit of multiple risk factor changes

CHD mortality at the population-level is usually caused by multiple risk factors acting simultaneously. Hence, part of the effect of one risk factor may be mediated through another. There are two approaches commonly used to account for the combined benefit of multiple risk factor changes: the cumulative risk reduction (CR) and the additive risk reduction (AR). The equations to measure the cumulative and additive effects of combining X risk factors are stated as:

$$CR = 1 - \prod_{x=1}^{X}(1 - |RRR_{xsi}|)$$

$$AR = \sum_{x=1}^{X}|RRR_{xsi}|$$

where RRR_{xsi} is the relative risk reduction by factor x for sex s and age group i

The ratio between CR and AR is defined as the adjustment factor (AF). This ratio then was used to adjust down the additive DPPs attributed to risk factor changes in order to account for the joint effect of risk factors.

The 70 age-sex-IMD specific adjustment factors are shown below.

	Deprivation quintile					
	IMDQ1	**IMDQ2**	**IMDQ3**	**IMDQ4**	**IMDQ5**	**England**
Men:						
25-34	0.9464	0.9449	0.9463	0.9462	0.9434	0.9453
35-44	0.9196	0.9169	0.9179	0.9126	0.9110	0.9153
45-54	0.9335	0.9278	0.9205	0.9193	0.9083	0.9219
55-64	0.8957	0.8957	0.8883	0.8851	0.8762	0.8886
65-74	0.8885	0.8843	0.8846	0.8817	0.8720	0.8827
75-84	0.9182	0.9146	0.9134	0.9214	0.9149	0.9162
85+	0.9561	0.9569	0.9525	0.9520	0.9582	0.9547
Women:						
25-34	0.8799	0.8872	0.8846	0.8787	0.8782	0.8809
35-44	0.9148	0.9119	0.9014	0.9034	0.8892	0.9038
45-54	0.9038	0.9013	0.8937	0.8777	0.8546	0.8865
55-64	0.8862	0.8896	0.8842	0.8703	0.8560	0.8780
65-74	0.8620	0.8569	0.8523	0.8363	0.8307	0.8479
75-84	0.8803	0.8869	0.8824	0.8778	0.8622	0.8779
85+	0.9394	0.9399	0.9409	0.9463	0.9386	0.9410
Overall	0.9089	0.9082	0.9045	0.9006	0.8924	0.9029

Table A: Age-sex IMD specific adjustment factors

2 Data and parameter sources

Input parameters	Type of distribution and functions (Mean, Standard error)	Source
Population		
Population counts and CHD deaths stratified by age, sex, and Index of Multiple Deprivation quintiles	Population counts (no error) Deaths expected in 2007 had CHD mortality rates in 2000 persisted (Poisson distribution)	Office for National Statistics Office for National Statistics (ONS): (*2000*: ICD9 410-414) (*2007*: ICD10 I20-I25)
Risk factors		
Mean estimates (pooled data; national estimates for 2000 and 2007) stratified by age, sex, and Index of Multiple Deprivation quintiles	SBP and total cholesterol): (Normal distribution: mean, SE of mean)	Health Survey for England
Beta coefficient: SBP stratified by age and sex	Normal distribution (mean, SE of mean): M < 45 (-0.036,0.004); M 45-54 (-0.035,0.004) M 55-64 (-0.032,0.003); M 65-74 (-0.027,0.003) M 75-84 (-0.021,0.002); M 85+ (-0.016,0.002) F < 55 (-0.046, 0.005); F 55-64 (-0.035,0.004) F 65-74 (-0.032,0.003); F 75-84 (-0.026,0.003) F 85+ (-0.019,0.002)	Prospective studies collaborative meta-analysis (2002) (6). Parameters on the log scale.
Beta coefficient: total cholesterol stratified by age and sex	Normal distribution (mean, SE of mean): M < 45 (-0.799,0.081); M 45-54 (-0.755,0.077) M 55-64 (-0.446,0.046); M 65-74 (-0.236,0.024) M 75-84 (-0.117,0.012); M 85+ (-0.083,0.009) F < 45 (-0.844,0.086); F 45-54 (-0.734,0.075) F 55-64 (-0.431,0.044); F 65-74 (-0.261,0.027) F 75-84 (-0.174,0.018); F 85+ (-0.051,0.005)	Prospective studies collaborative meta-analysis (2007) (7). Parameters on the log-scale.
Primary prevention therapies: Statins		
Treatment uptake stratified by age, sex, and Index of Multiple Deprivation quintiles	% never having had angina or heart attack and currently taking lipid lowering drugs prescribed by a doctor: (Beta distribution: cases, sample-size minus cases)	Health Survey for England
Case fatality rate	Sample size (n) = never having had angina or heart attack	Wijeysundera et al

stratified by age and sex	and currently taking lipid lowering drugs in 2006: Beta distribution (cases = n × CFR estimate, non-cases = n – cases)	(2010) (8)
Relative risk reduction: Statins stratified by sex	Ersatz RR function (RRR, SE ln(RRR)): M & F (0.35,0.396)	Pignone (2000) (9)
Primary prevention therapies: Treatments for high blood pressure		
Treatment uptake stratified by age, sex, and Index of Multiple Deprivation quintiles	% never having had angina or heart attack and currently taking medication specifically prescribed to treat high blood pressure: (Beta distribution: cases, sample-size minus cases)	Health Survey for England
Case fatality rate stratified by age and sex	Sample size (n) = never having had angina or heart attack and currently taking medication to lower blood pressure in 2006: Beta distribution (cases = n × CFR estimate, non-cases = n – cases)	Wijeysundera et al (2010) (63)
Relative risk reduction: Statins stratified by sex	Ersatz RR function (RRR, SE ln(RRR)): M & F (0.13,0.294)	Law (2003) (10)

Table B. Data sources and uncertainty analysis requirements

2.1. Uncertainty analysis: parameter distributions, functions and sources

We implemented stochastic uncertainty analysis in Excel using Ersatz (version 1.31 available at http://www.epigear.com), an add-in that allows probabilistic bootstrapping in Excel (5). Ersatz allows repeated random draws from specified distributions for input variables that are used to recalculate iteratively the model. It then calculates the 95% uncertainty intervals from the realised values of the output variable (deaths prevented or postponed). For the $IMPACT_{SEC}$ model, we calculated the uncertainty intervals based on 5000 draws taking the 95% uncertainty intervals as the 2.5^{th} and 97.5^{th} percentiles. Input variables taken from external sources (e.g. case fatality rates, beta coefficients and relative risk reductions) were randomly drawn from specified distributions but assumed constant across deprivation quintiles. Table B's second row records the type of distribution and associated functions for the input variables in the $IMPACT_{SEC}$ model associated to SBP and Cholesterol.

3 Tables by gender

3.1. Men

DPPS through changes in the population						
	England	IMD quintile 1	IMD quintile 2	IMD quintile 3	IMD quintile 4	IMD quintile 5
		Affluent				Deprived
Mean	5872	1041	1015	1121	1247	1449
95% LL	3029	495	411	510	675	912
95% UL	8593	1557	1591	1709	1785	1960
DPPS through changes in the treatments uptakes						
	England	IMD quintile 1	IMD quintile 2	IMD quintile 3	IMD quintile 4	IMD quintile 5
		Affluent				Deprived
Mean	3017	474	763	751	596	434
95% LL	1211	187	291	261	218	157
95% UL	7005	1017	1867	2144	1470	1028

Table C: CHD deaths prevented or postponed through medication and population changes in SBP and Cholesterol between 2000 and 2007 in England, stratified by deprivation quintiles

DPPS through SBP reduction						
Overall						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	4812	806	941	996	1014	1054
95% LL	2011	265	320	390	463	540
95% UL	7625	1356	1573	1598	1557	1549
Population wide changes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	4106	659	745	850	898	954
95% LL	1416	138	168	269	365	456
95% UL	6713	1165	1304	1414	1419	1442
Anti-hypertension treatment						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	705	147	196	146	116	100
95% LL	198	45	46	39	31	30
95% UL	1808	370	528	386	312	247

Table D: CHD deaths prevented or postponed through medication and population changes in SBP between 2000 and 2007 in England, stratified by deprivation quintiles

DPPS through Cholesterol reduction						
Overall						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	4078	709	836	875	829	829
95% LL	2150	400	365	371	414	498
95% UL	8149	1246	1905	2242	1681	1407
Population wide changes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	1766	381	270	271	349	495
95% LL	916	234	99	88	175	311
95% UL	2615	535	442	450	521	675
Statins treatment						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	2312	327	566	605	480	334
95% LL	684	85	155	159	130	83
95% UL	6184	861	1648	1992	1351	912

Table E: CHD deaths prevented or postponed through medication and population changes in cholesterol between 2000 and 2007 in England, stratified by deprivation quintiles

3.2. Women

DPPS through changes in the population						
	England	IMD quintile 1	IMD quintile 2	IMD quintile 3	IMD quintile 4	IMD quintile 5
		Affluent				Deprived
Mean	7380	1053	1652	1487	1495	1694
95% LL	3673	341	834	682	730	1062
95% UL	10669	1679	2370	2197	2175	2264
DPPS through changes in the treatments uptakes						
	England	IMD quintile 1	IMD quintile 2	IMD quintile 3	IMD quintile 4	IMD quintile 5
		Affluent				Deprived
Mean	4081	937	623	962	944	615
95% LL	1692	342	261	383	365	246
95% UL	8916	2402	1357	2250	2112	1494

Table F: CHD deaths prevented or postponed through medication and population changes in SBP and Cholesterol between 2000 and 2007 in England, stratified by deprivation quintiles

DPPS through SBP reduction						
Overall						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	8149	1412	1638	1733	1722	1644
95% LL	4422	696	822	917	955	1011
95% UL	11540	2064	2366	2475	2420	2218
Population wide changes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	7056	1202	1424	1471	1492	1467
95% LL	3446	513	628	701	745	854
95% UL	10329	1816	2136	2176	2161	2018
Anti-hypertension treatment						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	1093	210	215	262	229	177
95% LL	319	63	64	75	65	53
95% UL	2624	510	520	641	575	433

Table G: CHD deaths prevented or postponed through medication and population changes in SBP between 2000 and 2007 in England, stratified by deprivation quintiles

DPPS through Cholesterol reduction						
Overall						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	3313	577	637	717	717	665
95% LL	1069	18	298	179	171	304
95% UL	8202	2065	1335	2005	1904	1562
Population wide changes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	325	-149	228	16	2	227
95% LL	-315	-264	99	-123	-134	97
95% UL	996	-31	364	161	144	365
Statins treatment						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	2988	727	409	700	714	438
95% LL	922	190	115	197	199	123
95% UL	7822	2203	1095	2009	1905	1323

Table H: CHD deaths prevented or postponed through medication and population changes in cholesterol between 2000 and 2007 in England, stratified by deprivation quintiles

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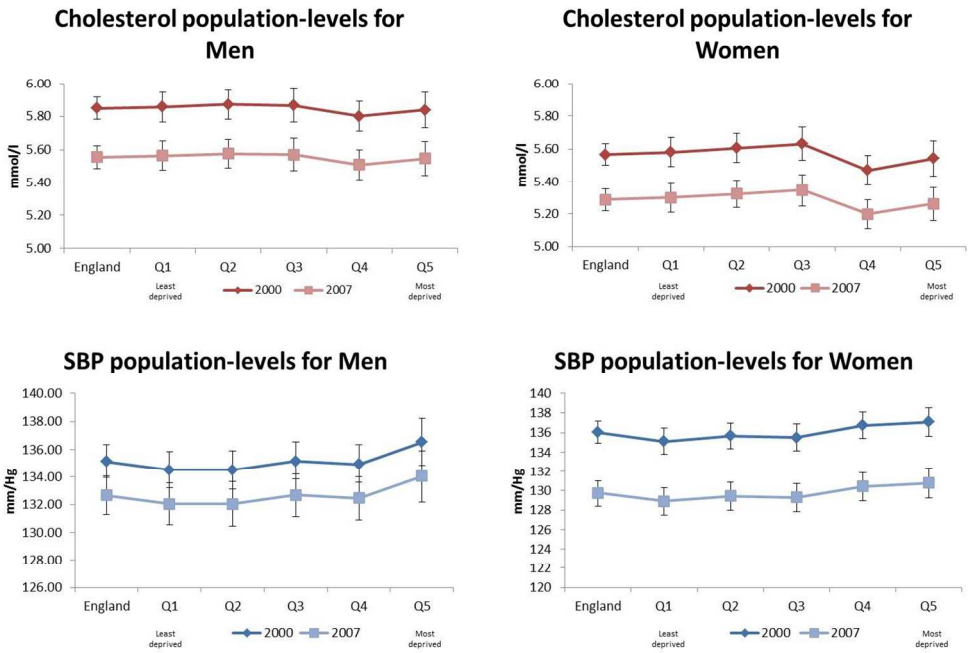

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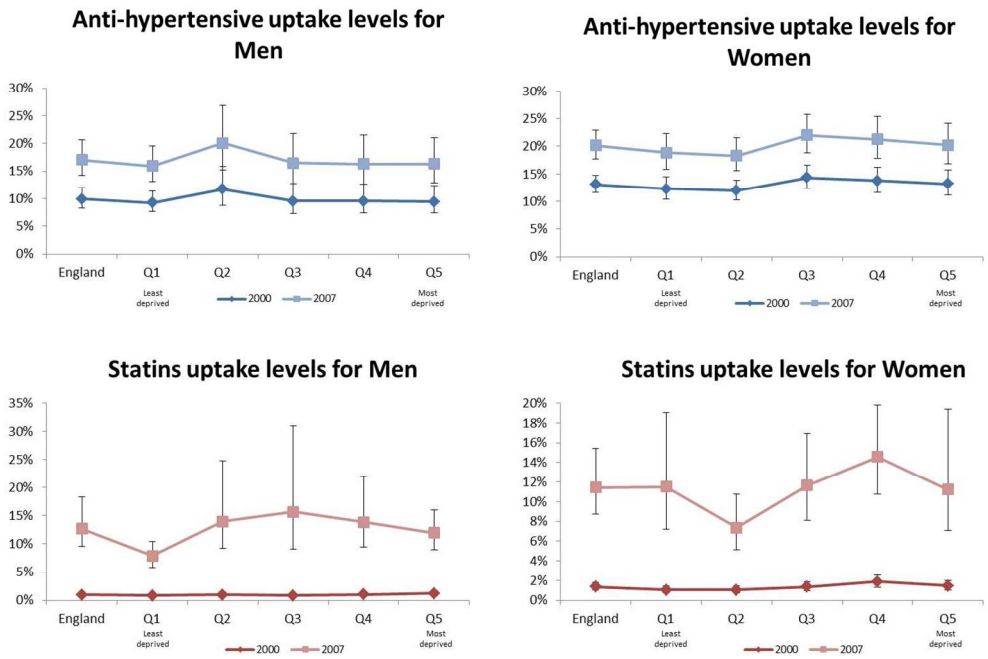

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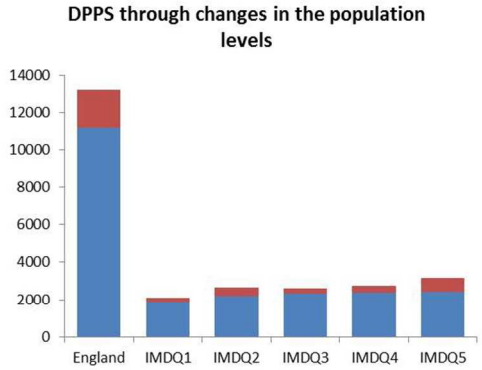

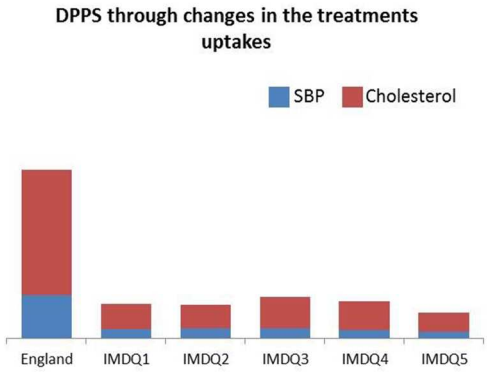

DPPs	England	IMD 1	IMD 2	IMD 3	IMD 4	IMD 5
Total	13253	2093	2666	2608	2742	3143
SBP	11162	1861	2168	2321	2391	2421
Cholesterol	2091	232	498	287	351	722

DPPs	England	IMD 1	IMD 2	IMD 3	IMD 4	IMD 5
Total	7098	1411	1386	1713	1539	1049
SBP	1798	357	411	408	345	277
Cholesterol	5300	1054	975	1305	1194	772

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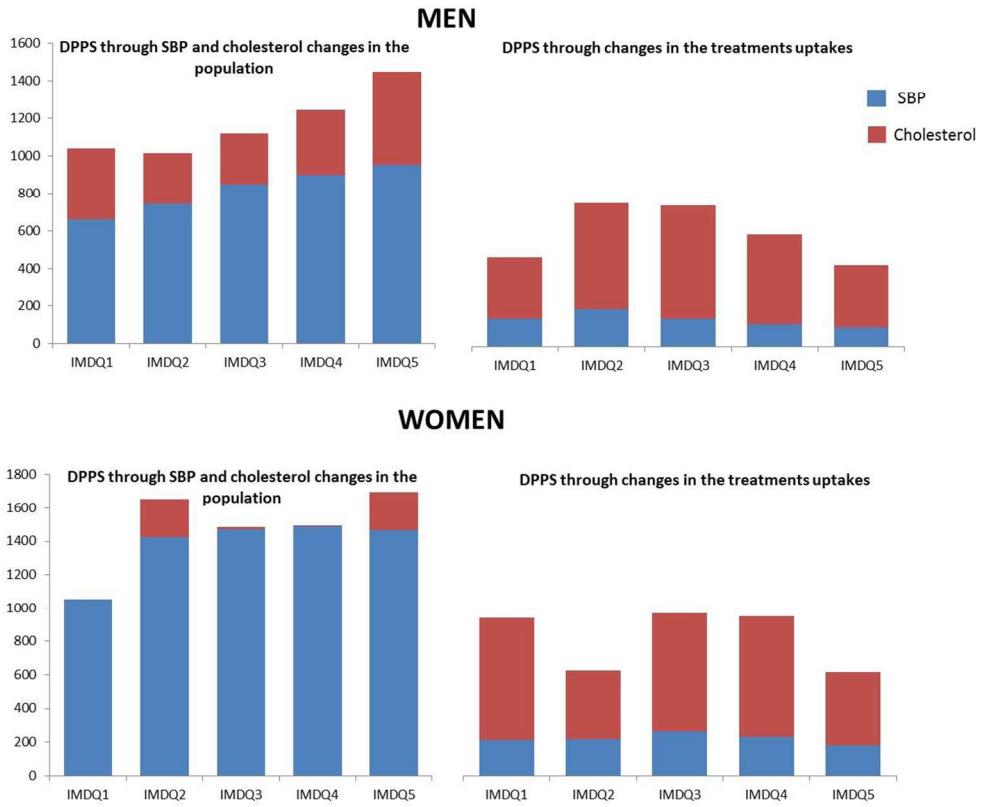

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The contribution of primary prevention medication and dietary change in coronary mortality reduction in England between 2000 and 2007: a modelling study

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The contribution of primary prevention medication and dietary change in coronary mortality reduction in England between 2000 and 2007: a modelling study

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Key words: Coronary heart disease mortality, inequalities, blood pressure, cholesterol, Rose's approach, primary prevention.

Abstract

Objective

To analyse the falls in coronary heart disease (CHD) mortality in England between 2000-2007 and quantify the relative contributions from preventive medications and population-wide changes in blood pressure (BP) and cholesterol levels, particularly exploring socioeconomic inequalities.

Design

A modelling study.

Setting

Sources of data included controlled trials and meta-analyses, national surveys and official statistics.

Participants

English population aged 25+ in 2000-2007.

Main outcome measures

Number of deaths prevented or postponed (DPPs) in 2007 by socioeconomic status. We used the $IMPACT_{SEC}$ model which applies the relative risk reduction quantified in previous randomised controlled trials and meta-analyses to partition the mortality reduction among specific treatments and risk factor changes.

Results

Between 2000-2007, approximately 20,400 DPPs were attributable to reductions in BP and cholesterol in the English population.

The substantial decline in BP was responsible for approximately 13,000 DPPs. Approximately 1,800 DPPs came from medications and some 11,200 DPPs from population-wide changes.

Reduction in population BP resulted prevented almost twofold more deaths in the most deprived quintile compared with the most affluent.

Reduction in cholesterol resulted in approximately 7,400 DPPs; approximately 5,300 DPPs were attributable to statin use and approximately 2,100 DPPs to population-wide changes.

Statins prevented almost 50% more deaths in the most affluent quintile compared with the most deprived. Conversely, population-wide changes in cholesterol prevented threefold more deaths in the most deprived quintile compared with the most affluent.

Conclusions

Population-wide secular changes in SBP and cholesterol levels helped to substantially reduce CHD mortality and the associated socioeconomic disparities. Mortality reductions were, in absolute terms, greatest in the most deprived quintiles, mainly reflecting their bigger initial burden of disease. Statins for high-risk individuals also made an important contribution but maintained socioeconomic inequalities. Our results strengthen the case for greater emphasis on preventive approaches, particularly population-based policies to reduce SBP and cholesterol.

Strengths

- This is the first IMPACT model to quantify the contributions of population risk factors and primary prevention treatments to recent changes in CHD mortality rates by socioeconomic quintiles.
- The datasets used for the model are representative of the English population and used deprivation scores for area of residence as an acceptable proxy indicator for socioeconomic status.
- Unlike the previous $IMPACT_{SEC}$ models, our study stratifies the analysis and results by gender. This allowed us to gain valuable new insights, for example changes in SBP and cholesterol population levels for women led to the highest number of DPPs for all quintiles. More surprisingly, the change in uptake levels for women in the least deprived quintile was almost as effective as the population-wide changes in SBP and cholesterol. This all suggests that any attempt to tackle the socioeconomic inequalities in CHD mortality should explicitly consider these gender differences.

Limitations

- Observed differences in CHD mortality by SES might reflect not material deprivation but other confounding and mediator factors such as alcohol consumption, obesity or ethnicity.
- Our risk factor effect data might still have some residual confounding. Statins and anti-hypertensive medication data is from surveys, therefore some misclassification bias might be present.
- We assumed that treatments and lifestyle changes have an immediate effect on CHD mortality, which might not be entirely true.
- We assumed that changes in the risk factors and treatment uptakes have equal effect across socioeconomic groups.
- Our adjustment to separate the DPPs from pharmacological versus non-pharmacological contributions to CHD mortality might overestimate medication benefit.
- Given the background of higher mortality and morbidity in the more deprived quintiles, DPPs might overestimate the actual health gain.
- The model was not able to explain around 14% of the total CHD mortality fall. One possible contributor might be the exclusion of other "upstream" cardiovascular risk factors, which might affect SES groups differentially.

Introduction

The UK, as many other industrialised countries, has experienced a remarkable 60% reduction in coronary heart disease (CHD) mortality since the 1970s. However CHD remains the leading cause of premature death (1).

Approximately one third of this initial CHD mortality reduction was attributable to treatments, and two thirds to reductions in major risk factors. The biggest contributions came from a large decline in smoking prevalence since the 1960s, and more recent reductions in blood pressure and cholesterol (2, 3).

The CHD mortality declines have demonstrated a changing relationship with socio-economic status (SES) (4-6). Initially, it demonstrated a positive relationship with SES (i.e. with affluence) (7). However, this has now reversed in more recent studies in the UK, US, New Zealand, Australia, and Scandinavia (8-10)

Risk factors have also demonstrated strong socioeconomic patterning. Substantial positive associations between lower SES and higher smoking prevalence and higher blood pressure levels have been reported in several studies (11-13). However, for cholesterol, the evidence has been less dramatic, with a higher intake of saturated fats among the more deprived populations reported in most studies (14-16), but not all (17-19). Socioeconomic differences in both risk factors may thus explain some of the CHD mortality gradients. Thus, any attempt to reduce the CHD burden and tackle the associated socioeconomic inequalities should explicitly consider these major risk factors (20).

Primary prevention medications to lower blood pressure and cholesterol have therefore been standard UK health policy for almost two decades. However, while their quantitative benefits to whole populations are accepted, their potential contributions to reduce inequalities are less clear (7,9,21,28,29,35,36).

The aim of this study was therefore to analyse the recent falls in CHD mortality and quantify the relative contributions from preventive medications and from population-wide changes in blood pressure and cholesterol levels, particularly exploring the potential effects on socioeconomic inequalities.

Methods

We used an extended version of the well-known IMPACT model to estimate the contributions of population-level risk factor changes and changes in treatment uptake on the CHD mortality decline in England between 2000 and 2007 for adults aged 25 and over, for two major risk factors, blood pressure and cholesterol (10).

The IMPACT model applies the relative risk reduction quantified in previous randomised controlled trials (RCT) and meta-analyses to estimate the mortality reduction attributable to a) temporal change in risk factor prevalence and b) net change over the period in the uptake of specific treatments in patients with each specific form of CHD. This previously validated deterministic cell-based model has been described in detail elsewhere (21, 22).

The extended version $IMPACT_{SEC}$ model (2) includes all the major CHD risk factors: smoking, systolic blood pressure (SBP), total cholesterol, body mass index (BMI), diabetes, physical inactivity and fruit and vegetable consumption. It also includes 45 medical and surgical treatments employed in nine different patient groups. Additionally, the model allows exploring the variation in CHD mortality trends by socioeconomic circumstances. Model inputs and outputs are stratified by the Index of Multiple Deprivation (IMD) quintiles as a proxy indicator of SES (14).

Our primary outcome measure was the mortality fall or more specifically, the total number of deaths prevented or postponed (DPPs), for each deprivation quintile, that can be attributed to either population-level risk factor changes in SBP and cholesterol, or changes in the uptake of anti-hypertensive and dyslipidaemia treatments. The DPPs in 2007 relative to 2000 are defined as the difference between the number of CHD expected deaths on 2007 (had age, sex, and SES quintile-specific CHD mortality rates in 2000 remained unchanged) and the observed figures.

To calculate the expected number of CHD deaths in 2007, we multiplied the age-sex-IMD quintile specific mortality rates from CHD in 2000 by the population counts for 2007 in that age-sex-IMD quintile stratum. Summing over all strata then yielded the expected number of deaths in 2007 had mortality rates remained unchanged. Population counts, CHD mortality rates and observed numbers of deaths used in this step, along with sources are enlisted in sections 3.1 and 3.2 of the Technical Appendix.

The first part of the $IMPACT_{SEC}$ model calculates the net benefit of statins and anti-hypertensive treatment in 2007. Firstly, we calculated the expected number of DPPs if statin and anti-hypertensive uptake rates in 2000 remained constant by multiplying the 2000 age-sex-IMD quintile specific treatments uptake levels by the population counts for 2000 in that age-sex-IMD quintile stratum, the one-year case fatality rate and the relative reduction in the case fatality rate estimated to be due to the administered treatment. We did the same for the expected number of DPPs in 2007 but now using 2007 age-sex-IMD quintile specific treatments uptake levels. The difference between the expected

number of DPPs (i.e. using the treatments uptake rates in 2000) and the estimated number DPPs (i.e. using the 2007 uptake rates) is the net benefit of treatments in 2007.

The uptake levels for anti-hypertensives and statins were defined as the prevalence of never having had angina or heart attack and currently taking medication specifically prescribed to treat high blood pressure or lipid lowering treatment respectively. Treatment uptake values, estimates of treatment efficacy (relative risk reductions) and age-sex specific case fatality rates, along with their sources are presented in sections 3.3-3.6 of the Technical Appendix.

The second part of the $IMPACT_{SEC}$ model estimates the number of DPPs related to changes in SBP and cholesterol levels in the population. To calculate DPPs from changes in risk factors, we used the regression approach, where the number of CHD deaths in 2000 were multiplied by the absolute change in risk factor level (absolute difference in the risk factors levels between 2000 and 2007), and by a regression beta coefficient quantifying the estimated relative change in CHD mortality that would result from a one-unit change in risk factor level. Risk factors mean levels and beta coefficients, along with their sources are presented in sections 3.7-3.9 of the Technical Appendix.

Recent reductions in CHD mortality have been the result of simultaneous change in multiple risk factors. Hence, part of the effect of one risk factor may be mediated through another. In this regard, we used a cumulative risk reduction adjustment factor (AF) to adjust down the DPPs attributed to multiple risk factors acting additively or separately, more details can be found in section 2.5 of the Technical Appendix.

Also we considered that some overlap between pharmacological and non-pharmacological contributions to risk factor DPPs occur. Therefore, to estimate the impact of population-wide reduction in total cholesterol due to non-pharmacological change only, we subtracted the estimated effect of cholesterol-lowering treatments uptakes levels change from the overall number of DPPs due to change in mean total cholesterol. A similar procedure was carried out for SBP and anti-hypertension treatments. For more details see section 2.6 of the Technical Appendix.

Finally, we implemented sensitivity analysis using the EXCEL add-in Ersatz software which allows Monte Carlo simulation. This allows us to calculate 95% uncertainty intervals (95% UI) for all outputs, based on 5000 draws from specified probabilistic distributions for the model input variables. The probabilistic distributions and their parameters used for the each of the input variables can be found in section 2.8 of the Technical Appendix.

More details on the methodology and worked examples can be found in the Technical Appendix.

Results

Systolic blood pressure (SBP) and cholesterol population levels

Figure 1 depicts the trends in population systolic blood pressure and cholesterol levels between 2000 and 2007, stratified by IMD quintiles and sex. Systolic blood pressure fell substantially between 2000 and 2007, by an average of 5.4 mmHg in women and by 2.5 mmHg in men. Total cholesterol also fell substantially (by approximately 0.20mmol/l), but equally in men and women.

There was no evidence of a social gradient, since the population factors levels were similar across IMD quintiles with no statistically significant difference between them.

Antihypertensive and statin treatment uptakes

Figure 2 depicts treatments uptakes between 2000 and 2007: there was a substantial increase in both treatment uptakes, especially statins. Uptakes levels of anti-hypertensive treatments and statins were remarkably equitable across quintiles for men and women, with no statistically significant differences between them.

Deaths prevented or postponed

There were approximately 38,000 fewer CHD deaths in 2007 than if 2000 mortality rates had persisted and been applied to 2007 population estimates for England. Our model was able to explain approximately 32,800 (86.3%) of these fewer deaths (see Table 1). Approximately 7,100 (95% UI, 3500 – 14,200) fewer deaths (19% of the total mortality reduction) were attributed to increases in the uptake levels of treatments for high blood pressure and raised cholesterol. Approximately 13,300 (8,500– 17,400) DPPs (35% of the mortality reduction) were attributed to population falls in blood pressure and cholesterol in asymptomatic individuals after subtracting the estimated effect of increases in treatment uptakes. The remaining 32% of the deaths prevented or postponed in our model were attributed to other risk factors and treatments.

Deaths prevented or postponed (DPP)						
	England	IMD quintile 1	IMD quintile 2	IMD quintile 3	IMD quintile 4	IMD quintile 5
		Affluent				Deprived
Mean	32770	5775	6745	7015	6870	6370
95% LL	25990	4430	5320	5420	5400	5100
95% UL	41550	7705	8515	9360	8765	7830

Table 1: CHD deaths prevented or postponed between 2000 and 2007 in England, stratified by deprivation quintiles.

Figures 3a and 3b show the number of deaths prevented or postponed from changes in the population mean levels of SBP and cholesterol (Figure 3a, left panel) and from changes in the treatment uptakes levels (Figure 3b, right panel). We can highlight some key aspects:

1) Population falls in SBP and cholesterol resulted in more DPPs than increases in uptake levels changes of anti-hypertensives and statins. 2) Most of the mortality reduction through population changes reflected falls in SBP rather than in cholesterol. 3) By contrast, most of the effect of treatment uptake levels changes was through increments in the uptake levels in statin use rather than antihypertensive use, reflecting the larger increase in statins use during the period of study (e.g. statin uptake rate in 2000 was around 1% compared to 12% in 2007 4) Substantial numbers of DPPs were observed in all social class groups. 5) The absolute effect of population changes on DPPs was larger among persons residing in the most deprived quintiles. 6) By contrast, the number of DPPs attributable to increases in uptake levels was remarkably equitable across SES groups. However, statin uptakes apparently postponed or prevented slightly more deaths in the most affluent quintile than in the most deprived quintile (Fig 3b).

Systolic blood pressure

Overall, SBP falls between 2000 and 2007 prevented or postponed approximately 13,000 (8,100 - 17,500) deaths (34.2% of the total mortality reduction). Approximately 1,800 (700-3,900) of those were attributable to anti-hypertension treatments (4.7% of the total mortality reduction) and some 11,200 DPPs (6,500-15,100), over six fold more, were attributable to population-wide SBP changes (29.5% of the total mortality reduction). Substantially more DPPs through population-wide changes occurred in the most deprived 2,400 (1,600-3,100) compared with the most affluent quintiles: 1,800 (1,000-2,600). Thus population-wide changes apparently helped to reduce inequalities in absolute terms. Conversely, changes in treatment uptake levels demonstrated the opposite effect, since more deaths were prevented in the most affluent quintile (360 DPPs) compared to the most deprived (280 DPPs). However in both cases, SES differences were not statistically significant. Detailed outputs with uncertainty intervals can be found in section 4 of the Technical Appendix.

Cholesterol

Overall, cholesterol falls between 2000 and 2007 resulted in approximately 7,400 (3,900-14,500) fewer deaths (19.5% of the total mortality reduction) (Table 6). This total comprised some 5,300 (2,100-12,300) fewer deaths (13.9% of the total mortality reduction) attributable to statin medications and approximately 2,100 (1,000-3,200) fewer deaths (5.5% of the total mortality reduction) attributable to population-wide falls in cholesterol. Statin medications prevented some 1,100 (400-2,700) deaths in the most affluent quintile compared to approximately 800 (300-1,900) DPPs in the most deprived quintile. Conversely, population changes in cholesterol resulted in approximately 700 (500-1,000) DPPs in the most deprived quintile and some 200 (40-400) DPPs in the most affluent quintile. However, like SBP there was no a clear SES gradient. Section 4 of the Technical Appendix provides detailed outputs with uncertainty intervals.

Gender differences

Figure 4 shows the number of deaths prevented or postponed in men and women, from falls in the population mean levels of SBP and cholesterol (Figure 4a, left panels) and from increases in the treatment uptakes levels (Figure 4b, right panels). For men, although most of the mortality reduction came from population falls in SBP, cholesterol reductions have also a considerable larger effect in reducing mortality compared to women (four times higher). By contrast, the number of DPPs due to increases in treatment uptake in men appeared remarkably equitable across SES groups.

For women, the impressive reduction in SBP mean level between 2000 and 2007, contributed the most to the total mortality reduction and in all quintiles, whereas population level reductions of cholesterol had a smaller benefit. Moreover, the joint benefit of increasing treatment uptakes (antihypertensive and statins) in women appeared to have an important effect: for example, in the most affluent quintile (IMDQ1) the reduction in DPPs due to the increase in uptakes for women was almost as effective as the population-wide falls in both sexes for that quintile.

However, in terms of differences between men and women, the results of the uncertainty analysis suggest that these are not significant in statistical terms. More detailed outputs split by gender can be found in the section 5 of Technical Appendix.

Discussion

Coronary heart disease mortality in England fell by a remarkable 34% between 2000 and 2007. This represents an impressive 38,000 fewer deaths from CHD in 2007 than if the 2000 mortality rates had persisted. Reductions in major cardiovascular risk factors of blood pressure and cholesterol explained almost two thirds of this large mortality fall.

Blood pressure trends

Declines in the population blood pressure level made the largest contribution to the overall fall in CHD mortality. In contrast, anti-hypertension treatments produced only modest benefits. Firstly, because the baseline CHD event rate was low in asymptomatic individuals (≤ 1% per year) yielding only a small reduction of the attributable risk during the period of study (24). Secondly, treatment efficacy is low and thirdly blood pressure control is still poor (adherence levels to medication are around 60%) (7), leading in conjunction to a substantial residual risk (21, 23).

Cholesterol trends

Population-wide falls in cholesterol levels averted more deaths in the most deprived quintiles, reflecting similar absolute falls but much higher baseline mortality rates. The increase in the uptake of statins between 2000 and 2007 made an even greater contribution to the overall mortality fall: two fold greater than the change in population cholesterol (16% versus 6%), and with equitable benefits across all five SES groups.

Comparisons with other studies

Our results are consistent with previous analyses in the UK and around the world, supporting the importance of this study beyond England. Using the IMPACT model to examine contributions to the overall reductions in CHD mortality in England and Wales population between 1981 and 2000, Unal, Critchley (3) reported a higher contribution from blood pressure changes (compared to cholesterol). Some 76% of this contribution was attributable to population-wide changes rather than anti-hypertensive medications. IMPACT analyses carried out in the US and Irish populations between 1980-2000 and 1985-2000 likewise observed substantially greater benefits attributable to secular changes in risk factors rather than treatments (22, 24).

The analysis by DeWilde, Carey (25) suggested that reported blood pressure treatments were responsible only for the 25% of 5mmHg reduction in SBP during the period 1994-2009 for England.

Emberson et al Emberson, Whincup (26) applied a very different methodology using evidence from randomised control trials and cohort studies to analyse the effectiveness of population-wide changes in risk factor levels against the high risk individual approach. Their findings were entirely consistent

with ours. They concluded that a mere 10% reduction in population-wide blood pressure and cholesterol levels might achieve a 45% reduction in cardiac events in the long term. Whereas it would be need to provide treatment to approximately 26% of the UK population in high risk to achieve a only a 34% reduction in cardiac events. The US CHD policy model likewise reported that population-wide reductions of salt intake (3 g per day) might prevent between 44,000 and 90,000 deaths (27).

Strengths & limitations

This is the first IMPACT model to quantify the contributions of population risk factors and primary prevention treatments to recent changes in CHD mortality rates by socioeconomic quintiles.

The datasets used for the model are representative of the English population and used deprivation scores for area of residence as an acceptable proxy indicator for socioeconomic status. This allowed a sufficient sample size to quantify the effect of risk factor modification through changes in population-wide risk factor levels and treatment uptake.

Unlike, the previous IMPACT$_{SEC}$ models (Bajekal, Scholes (2) and Scholes, Bajekal (28)), our study stratifies the analysis and results by gender. This allowed us to gain valuable new insights, for example changes in SBP and cholesterol population levels for women led to the highest number of DPPs for all quintiles. More surprisingly, the change in uptake levels for women in the least deprived quintile was almost as effective as the population-wide changes in SBP and cholesterol. This all suggests that any attempt to tackle the socioeconomic inequalities in CHD mortality should explicitly consider these gender differences.

However, our study limitations should also be acknowledged. Firstly, the area-level categorisation may not be representative of individual circumstances. Furthermore, observed SES differences in CHD mortality might reflect not material deprivation but other confounding and mediator factors such as alcohol consumption, obesity or ethnicity. However, the IMD is a comprehensive multi-dimensional construct of socioeconomic status made up of seven domains, and based on small geographical areas (less than 1500 residents) called Lower Level Super Output Areas (LSOAs). The advantage of using LSOAs is that their smaller geographical sizes also allow for a more detailed knowledge of deprived areas.

Our risk factor effect data might still have some residual confounding. Statins and anti-hypertensive medication data is from surveys, therefore some misclassification bias might be present.

We assumed that treatments and lifestyle changes have an immediate effect on CHD mortality, which might not be entirely true. However, Capewell and O'Flaherty (29, 30) pointed out evidence from clinical trials and policy interventions which consistently suggests that changes in diet and lifestyle across entire populations can be rapidly followed by dramatic declines in mortality.

We assumed that changes in the risk factors and treatment uptakes have equal effect across socioeconomic groups. However, the benefits of falls in risk factors or increases in treatment uptakes may be higher in more affluent groups (2). This may partly explain the faster rates of CHD mortality decline in the most affluent quintiles as Bajekal, Scholes (10) pointed out. Likewise, we assumed that the relative risk reduction due to treatments remained constant from 2000 to 2007.

We simply subtracted the mortality gains from increasing uptake levels of statins from the overall gains due to reductions in total cholesterol to estimate the impact of population-wide reduction in total cholesterol due to non-pharmacological change only. This mutually exclusive adjudication of cause adjustment might overestimate medication benefit.

Given the background of higher mortality and morbidity in the more deprived quintiles, DPPs might overestimate the actual health gain, as we don't know the additional life span gained by preventing a specific death at a specific time. This might result in a lesser reduction in inequalities than DPPs alone would suggest.

Finally, our model was not able to explain around 14% of the total CHD mortality fall between 2000 and 2007. One possible contributor might be the exclusion of other "upstream" cardiovascular risk factors, which might affect SES groups differentially, for example, psychosocial stress (31).

Implications for public health and clinical care

This study shows that population-wide secular falls in blood pressure and cholesterol have substantially helped to decrease CHD mortality and reduce the associated socioeconomic disparities in absolute terms. Furthermore, as we discussed earlier, there is an increasing body of evidence to support the use of population-wide approaches to reduce CHD risk factors. Mackenbach, Lingsma (32) recently evaluated 22 successful preventive interventions in the Netherlands. Approximately 75% of the health gains during the period 1970-2010 were achieved by a population approach and just 25% by a high risk individual approach.

In the UK, the population-wide fall in blood pressure is consistent with the recent successful implementation of policies to reduce salt intake. Similar trends have been reported in other developed countries (21, 23). There are also several international examples where policy interventions have proven to be effective at achieving significant reductions in saturated fats, trans-fats and calories in processed foods and takeaway meals (27, 33-35). However policies to reduce saturated fats and trans-fats have thus far been neglected in the UK (36).

Conversely, targeting high-risk individuals with medication appears less effective and may also widen socioeconomic inequalities in CHD mortality (37,38). Any intervention that requires people to mobilise their own resources (material and psychological) will understandably favour those who have

greater resources (37) and thus widen social inequalities. Thus, those with the poorest health will benefit the least from such interventions (38).

However, there is no simple choice between either population-based or high risk strategies to reduce CHD mortality. The approaches are complementary in delivering the greatest public health benefit (39, 40). It is, however, clear that individual-based treatment strategies can afford only modest reductions in mortality compared with addressing risk factors population wide.

Severely limited health care budgets are now forcing planning systems to consider how best to allocate future resources. Our results strengthen the case for greater emphasis on preventive approaches, particularly population based policies to reduce blood pressure and cholesterol. Such strategies might be more powerful, rapid, cost-effective, and equitable than additional preventive medications (36).

Author contributions

MGC drafted the manuscript, analysed the results and conducted the uncertainty analysis in collaboration with S Capewell, M O'Flaherty and R. Ahmed. R. Ahmed conducted the initial literature review and initial set up of the model in collaboration with S Capewell. N Hawkins, S Scholes, E Wilkinson, J Lucy contributed to the interpretation of the results and to the drafting and finalisation of the manuscript

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Details of funding

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Data sharing statement

Data, $IMPACT_{SEC}$ spreadsheet and detailed results are available upon request by emailing Maria Guzman-Castillo.

Role of sponsor

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Transparency declaration

The lead author Maria Guzman Castillo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been reported.

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The contribution of primary prevention medication and dietary change in coronary mortality reduction in England between 2000 and 2007: a modelling study

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Abstract

Objective

To analyse the falls in coronary heart disease (CHD) mortality in England between 2000-2007 and quantify the relative contributions from preventive medications and from population-wide changes in blood pressure (BP) and cholesterol levels, particularly exploring socioeconomic inequalities.

Design

A modelling study.

Setting

Sources of data included controlled trials and meta-analyses, national surveys and official statistics.

Participants

Population aged 25+ in England in 2000-2007.

Main outcome measures

Number of deaths prevented or postponed (DPPs) in 2007 by socioeconomic status. We used the $IMPACT_{SEC}$ model which applies the relative risk reduction quantified in previous randomised controlled trials and meta-analyses to partition the mortality reduction among specific treatments and risk factor changes.

Results

Between 2000-2007, approximately 22,500 DPPs were attributable to reductions in BP and cholesterol in the English population.

The substantial decline in BP was responsible for approximately 13,000 DPPs. Approximately 1,800 DPPs came from medications and some 11,200 DPPs from population-wide changes.

Reduction in population BP resulted in approximately 2,400 DPPs in the most deprived quintile compared with 1,900 DPPs in the most affluent.

Reduction in cholesterol resulted in approximately 7,400 DPPs; approximately 5,300 DPPs were attributable to statin use and approximately 2,100 DPPs to population-wide changes.

Statins prevented more deaths in the most affluent quintile (1,100 DPPs) compared with the most deprived (800 DPP). Conversely, population-wide changes in cholesterol prevented threefold more deaths in the most deprived quintile (700 DPPs) compared with the most affluent (230 DPPs).

Conclusions

Population-wide secular changes in blood pressure and cholesterol levels helped to substantially reduce CHD mortality and the associated socioeconomic disparities. Mortality reductions were, in absolute terms, greatest in the most deprived quintiles, mainly reflecting their bigger initial burden of disease. Statins for high-risk individuals also made an important contribution but maintained socioeconomic inequalities. Our results strengthen the case for greater emphasis on preventive approaches, particularly population-based policies to reduce blood pressure and cholesterol.

Strengths

- This is the first IMPACT model to quantify the contributions of population risk factors and primary prevention treatments to recent changes in CHD mortality rates by socioeconomic quintiles.
- The datasets used for the model are representative of the English population and used deprivation scores for area of residence as an acceptable proxy indicator for socioeconomic status.
- Unlike the previous $IMPACT_{SEC}$ models (Bajekal, Scholes (1) and Scholes, Bajekal (2)), our study stratifies the analysis and results by gender. This allowed us to gain valuable new insights, for example changes in SBP and cholesterol population levels for women led to the highest number of DPPs for all quintiles. More surprisingly, the change in uptake levels for women in the least deprived quintile was almost as effective as the population-wide changes in SBP and cholesterol. This all suggests that any attempt to tackle the socioeconomic inequalities in CHD mortality should explicitly consider these gender differences.

Limitations

- Observed differences in CHD mortality by SES might reflect not material deprivation but other confounding and mediator factors such as alcohol consumption, obesity or ethnicity.
- Our risk factor effect data might still have some residual confounding. Statins and anti-hypertensive medication data is from surveys, therefore some misclassification bias might be present.
- We assumed that treatments and lifestyle changes have an immediate effect on CHD mortality, which might not be entirely true.
- We assumed that changes in the risk factors and treatment uptakes have equal effect across socioeconomic groups.
- Our adjustment to separate the DPPs from pharmacological versus non-pharmacological contributions to CHD mortality might overestimate medication benefit.
- Given the background of higher mortality and morbidity in the more deprived quintiles, DPPs might overestimate the actual health gain.
- The model was not able to explain around 14% of the total CHD mortality fall. One possible contributor might be the exclusion of other "upstream" cardiovascular risk factors, which might affect SES groups differentially.

Introduction

The UK, as many other industrialised countries, has experienced a remarkable 60% reduction in coronary heart disease (CHD) mortality since the 1970s. However CHD remains the leading cause of premature death (3).

Approximately one third of this initial CHD mortality reduction was attributable to treatments, and two thirds to reductions in major risk factors. The biggest contributions came from a large decline in smoking prevalence since the 1960s, and more recent reductions in blood pressure and cholesterol (1, 4).

The CHD mortality declines have demonstrated a changing relationship with socio-economic status (SES) (5-7). Initially, it demonstrated a positive relationship with SES (i.e. with affluence) (8). However, this has now reversed in more recent studies in the UK, US, New Zealand, Australia, and Scandinavia (9-11)

Risk factors have also demonstrated strong socioeconomic patterning. Substantial positive associations between lower SES and higher smoking prevalence and higher blood pressure levels have been reported in several studies (12-14). However, for cholesterol, the evidence has been less dramatic, with a higher intake of saturated fats among the more deprived populations reported in most studies (15-17), but not all (18-20). Socioeconomic differences in both risk factors may thus explain some of the CHD mortality gradients. Thus, any attempt to reduce the CHD burden and tackle the associated socioeconomic inequalities should explicitly consider these major risk factors (21).

Primary prevention medications to lower blood pressure and cholesterol have therefore been standard UK health policy for almost two decades. However, while their quantitative benefits to whole populations are accepted, their potential contributions to reduce inequalities are less clear (7,9,21,28,29,35,36).

The aim of this study was therefore to analyse the recent falls in CHD mortality and quantify the relative contributions from preventive medications and from population-wide changes in blood pressure and cholesterol levels, particularly exploring the potential effects on socioeconomic inequalities.

Methods

We used an extended version of the well-known IMPACT model to estimate the contributions of population-level risk factor changes and changes in treatment uptake on the CHD mortality decline in England between 2000 and 2007 for adults aged 25 and over, for two major risk factors, blood pressure and cholesterol (11).

The IMPACT model applies the relative risk reduction quantified in previous randomised controlled trials (RCT) and meta-analyses to estimate the mortality reduction attributable to a) temporal change in risk factor prevalence and b) net change over the period in the uptake of specific treatments in patients with each specific form of CHD. This previously validated deterministic cell-based model has been described in detail elsewhere (22, 23).

The extended version $IMPACT_{SEC}$ model (1) includes all the major CHD risk factors: smoking, systolic blood pressure (SBP), total cholesterol, body mass index (BMI), diabetes, physical inactivity and fruit and vegetable consumption. It also includes 45 medical and surgical treatments employed in nine different patient groups. Additionally, the model allows exploring the variation in CHD mortality trends by socioeconomic circumstances. Model inputs and outputs are stratified by the Index of Multiple Deprivation (IMD) quintiles as a proxy indicator of SES (15).

Our primary outcome measure was the mortality fall or more specifically, the total number of deaths prevented or postponed (DPPs), for each deprivation quintile, that can be attributed to either population-level risk factor changes in SBP and cholesterol, or changes in the uptake of anti-hypertensive and dyslipidaemia treatments. The DPPs in 2007 relative to 2000 are defined as the difference between the number of CHD expected deaths on 2007 (had age, sex, and SES quintile-specific CHD mortality rates in 2000 remained unchanged) and the observed figures.

To calculate the expected number of CHD deaths in 2007, we multiplied the age-sex-IMD quintile specific mortality rates from CHD in 2000 by the population counts for 2007 in that age-sex-IMD quintile stratum. Summing over all strata then yielded the expected number of deaths in 2007 had mortality rates remained unchanged. Population counts, CHD mortality rates and observed numbers of deaths used in this step, along with sources are enlisted in sections 3.1 and 3.2 of the Technical Appendix.

The first part of the $IMPACT_{SEC}$ model calculates the net benefit of statins and anti-hypertensive treatment in 2007. Firstly, we calculated the expected number of DPPs from statins and anti-hypertensive treatment, if the uptake rates in 2000 remained constant, by multiplying the 2000 age-sex-IMD quintile specific treatments uptake levels by the population counts for 2000 in that age-sex-IMD quintile stratum, the one-year case fatality rate and the relative reduction in the case fatality rate estimated to be due to the administered treatment. We did the same for the expected number of DPPs in 2007 but now using 2007 age-sex-IMD quintile specific treatments uptake levels. The difference

between the expected number of DPPs (i.e. using the treatments uptake rates in 2000) and the estimated number DPPs (i.e. using the 2007 uptake rates) is the net benefit of treatments in 2007.

The uptake levels for anti-hypertensives and statins were defined as the prevalence of never having had angina or heart attack and currently taking medication specifically prescribed to treat high blood pressure or lipid lowering treatment respectively. Treatment uptake values, estimates of treatment efficacy (relative risk reductions) and age-sex specific case fatality rates, along with their sources are presented in sections 3.3-3.6 of the Technical Appendix.

The second part of the $IMPACT_{SEC}$ model estimates the number of DPPs related to changes in SBP and cholesterol levels in the population. To calculate DPPs from changes in risk factors, we used the regression approach, where the number of CHD deaths in 2000 were multiplied by the absolute change in risk factor level (absolute difference in the risk factors levels between 2000 and 2007), and by a regression beta coefficient quantifying the estimated relative change in CHD mortality that would result from a one-unit change in risk factor level. Risk factors mean levels and beta coefficients, along with their sources are presented in sections 3.7-3.9 of the Technical Appendix.

Recent reductions in CHD mortality have been the result of simultaneous change in multiple risk factors. Hence, part of the effect of one risk factor may be mediated through another. In this regard, we used a cumulative risk reduction adjustment factor (AF) to adjust down the DPPs attributed to multiple risk factors acting additively or separately, more details can be found in section 2.5 of the Technical Appendix.

Also we considered that some overlap between pharmacological and non-pharmacological contributions to risk factor DPPs occur. Therefore, to estimate the impact of population-wide reduction in total cholesterol due to non-pharmacological change only, we subtracted the estimated effect of cholesterol-lowering treatments uptakes levels change from the overall number of DPPs due to change in mean total cholesterol. A similar procedure was carried out for SBP and anti-hypertension treatments. For more details see section 2.6 of the Technical Appendix.

Finally, we implemented sensitivity analysis using the EXCEL add-in Ersatz software which allows Monte Carlo simulation. This allows us to calculate 95% uncertainty intervals (95% UI) for all outputs, based on 5000 draws from specified probabilistic distributions for the model input variables. The probabilistic distributions and their parameters used for the each of the input variables are shown in section 2.8 of the Technical Appendix.

More details on the methodology with worked examples can be found in the Technical Appendix.

Results

Systolic blood pressure (SBP) and cholesterol population levels

Figures 1 depicts the trends in population systolic blood pressure and cholesterol levels between 2000 and 2007, stratified by IMD quintiles and sex. Systolic blood pressure fell substantially between 2000 and 2007, by an average of 5.4 mmHg in women and by 2.5 mmHg in men. Total cholesterol also fell substantially (by approximately 0.20mmol/l), but equally in men and women.

There was no evidence of a social gradient, since the population factors levels were similar across IMD quintiles with no statistically significant difference between them.

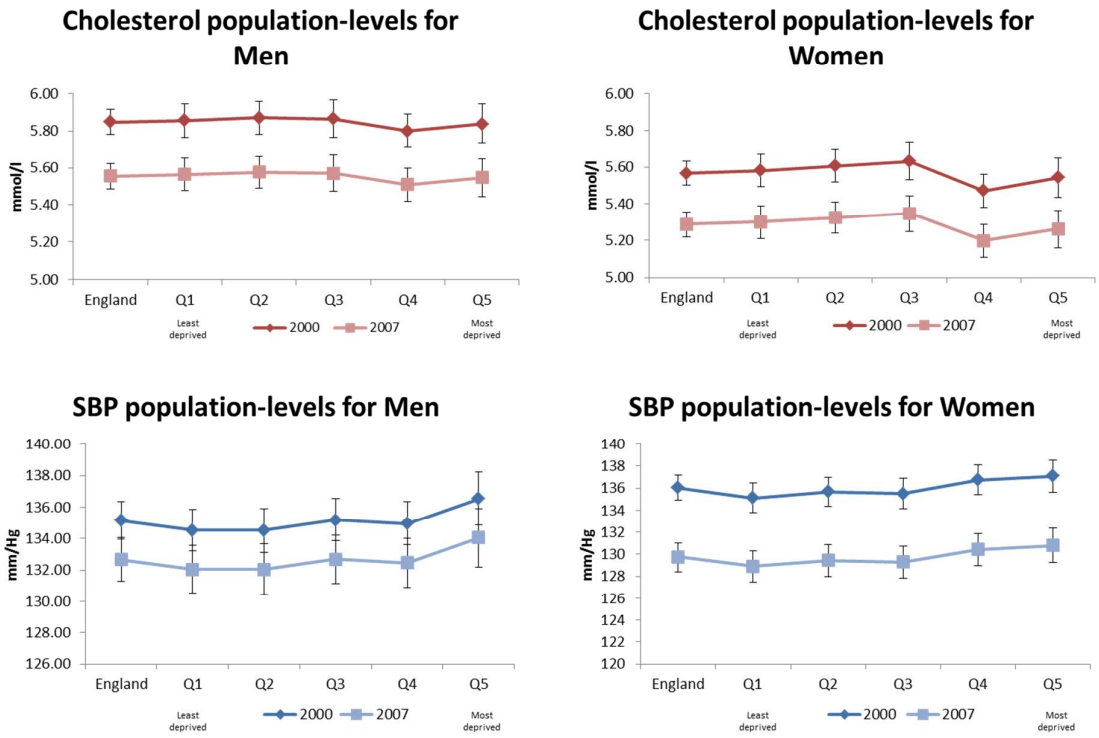


Figure 1: Mean values of SBP and cholesterol between 2000 and 2007 for England and stratified by deprivation quintiles and sex (95% UI).

Antihypertensive and statin treatment uptakes

Figure 2 depicts treatments uptakes between 2000 and 2007: there was a substantial increase in both treatment uptakes, especially statins. Uptakes levels of anti-hypertensive treatments and statins were remarkably equitable across quintiles for men and women, with no statistically significant differences between them.

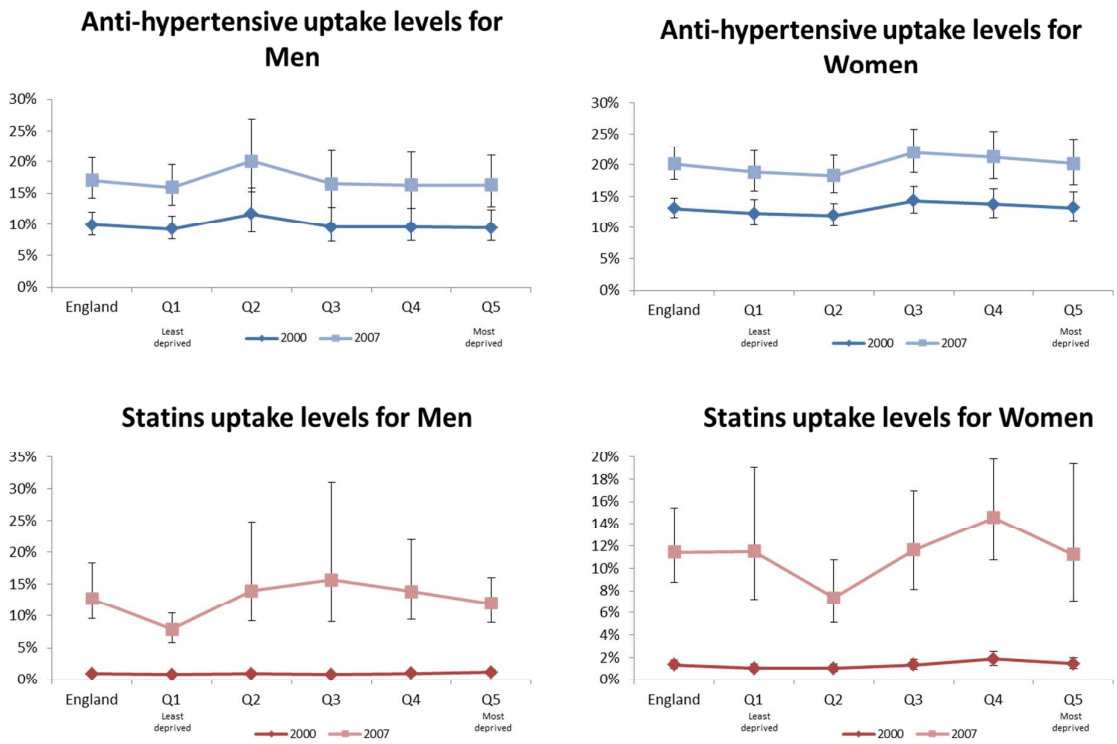


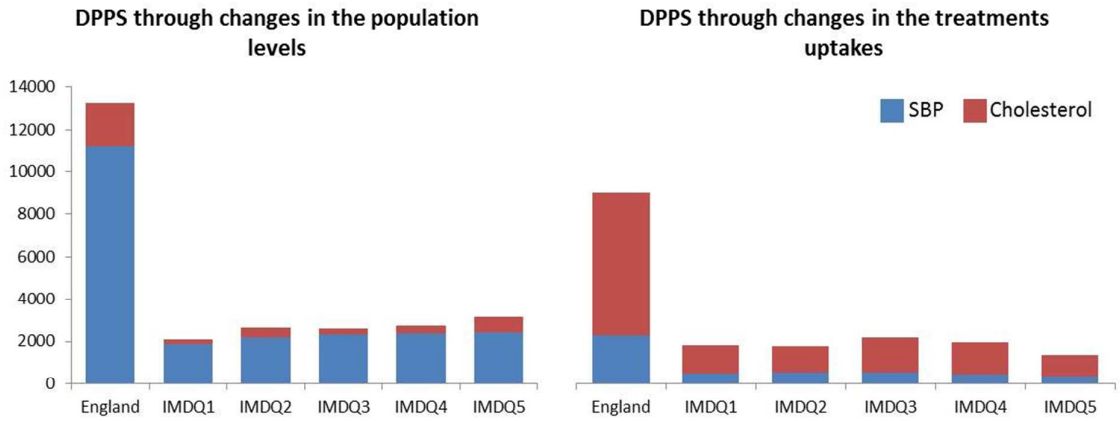
Figure 2: Uptake levels and proportion change in treatment uptake between 2000 and 2007 for England stratified by deprivation quintiles (95% UI).

Deaths prevented or postponed

There were approximately 38,000 fewer CHD deaths in 2007 than if 2000 mortality rates had persisted and been applied to 2007 population estimates for England. Our model was able to explain approximately 32,800 (86.3%) of these fewer deaths (see Table 1). Approximately 7,100 (95% UI, 3500 – 14,200) fewer deaths (19% of the total mortality reduction) were attributed to increases in the uptake levels of treatments for high blood pressure and raised cholesterol. Approximately 13,300 (8,500– 17,400) DPPs (35% of the mortality reduction) were attributed to population falls in blood pressure and cholesterol in asymptomatic individuals after subtracting the estimated effect of increases in treatment uptakes. The remaining 32% of the deaths prevented or postponed in our model were attributed to other risk factors and treatments.

Deaths prevented or postponed (DPP)						
	England	IMD quintile 1	IMD quintile 2	IMD quintile 3	IMD quintile 4	IMD quintile 5
		Affluent				Deprived
Mean	32770	5775	6745	7015	6870	6370
95% LL	25990	4430	5320	5420	5400	5100
95% UL	41550	7705	8515	9360	8765	7830

Table 1: CHD deaths prevented or postponed between 2000 and 2007 in England, stratified by deprivation quintiles.



DPPs	England	IMD 1	IMD 2	IMD 3	IMD 4	IMD 5
Total	13253	2093	2666	2608	2742	3143
SBP	11162	1861	2168	2321	2391	2421
Cholesterol	2091	232	498	287	351	722

DPPs	England	IMD 1	IMD 2	IMD 3	IMD 4	IMD 5
Total	7098	1411	1386	1713	1539	1049
SBP	1798	357	411	408	345	277
Cholesterol	5300	1054	975	1305	1194	772

Figures 3a and 3b: Number of deaths prevented or postponed (DPPs) between 2000 and 2007 in England attributable to changes in the population in SBP and cholesterol (Fig 3a, left panel), changes in uptakes levels for anti-hypertensive treatments and statins (Fig 3b, right panel); stratified by deprivation quintiles

Figures 3a and 3b show the number of deaths prevented or postponed from changes in the population mean levels of SBP and cholesterol (Figure 3a, left panel) and from changes in the treatment uptakes levels (Figure 3b, right panel). We can highlight some key aspects:

1) Population falls in SBP and cholesterol resulted in more DPPs than increases in uptake levels changes of anti-hypertensives and statins. 2) Most of the mortality reduction through population changes reflected falls in SBP rather than in cholesterol. 3) By contrast, most of the effect of treatment uptake levels changes was through increments in the uptake levels in statin use rather than antihypertensive use, reflecting the larger increase in statins use during the period of study (e.g. statin uptake rate in 2000 was around 1% compared to 12% in 2007 4) Substantial numbers of DPPs were

observed in all social class groups. 5) The absolute effect of population changes on DPPs was larger among persons residing in the most deprived quintiles. 6) By contrast, the number of DPPs attributable to increases in uptake levels was remarkably equitable across SES groups. However, statin uptakes apparently postponed or prevented slightly more deaths in the most affluent quintile than in the most deprived quintile (Fig 3b).

Systolic blood pressure

Overall, SBP falls between 2000 and 2007 prevented or postponed approximately 13,000 (8,100 - 17,500) deaths (34.2% of the total mortality reduction). Approximately 1,800 (700-3,900) of those were attributable to anti-hypertension treatments (4.7% of the total mortality reduction) and some 11,200 DPPs (6,500-15,100), over six fold more, were attributable to population-wide SBP changes (29.5% of the total mortality reduction). Substantially more DPPs through population-wide changes occurred in the most deprived 2,400 (1,600-3,100) compared with the most affluent quintiles: 1,800 (1,000-2,600). Thus population-wide changes apparently helped to reduce inequalities in absolute terms. Conversely, changes in treatment uptake levels demonstrated the opposite effect, since more deaths were prevented in the most affluent quintile compared to the most deprived. However in both cases, SES differences were not statistically significant. Detailed outputs with uncertainty intervals can be found in section 4 of the Technical Appendix.

Cholesterol

Overall, cholesterol falls between 2000 and 2007 resulted in approximately 7,400 (3,900-14,500) fewer deaths (19.5% of the total mortality reduction) (Table 6). This total comprised some 5,300 (2,100-12,300) fewer deaths (13.9% of the total mortality reduction) attributable to statin medications and approximately 2,100 (1,000-3,200) fewer deaths (5.5% of the total mortality reduction) attributable to population-wide falls in cholesterol. Statin medications prevented some 1,100 (400-2,700) deaths in the most affluent quintile compared to approximately 800 (300-1,900) DPPs in the most deprived quintile. Conversely, population changes in cholesterol resulted in approximately 700 (500-1,000) DPPs in the most deprived quintile and some 200 (40-400) DPPs in the most affluent quintile. However, like SBP there was no a clear SES gradient. (section 4 of the Technical Appendix provides detailed outputs with uncertainty intervals).

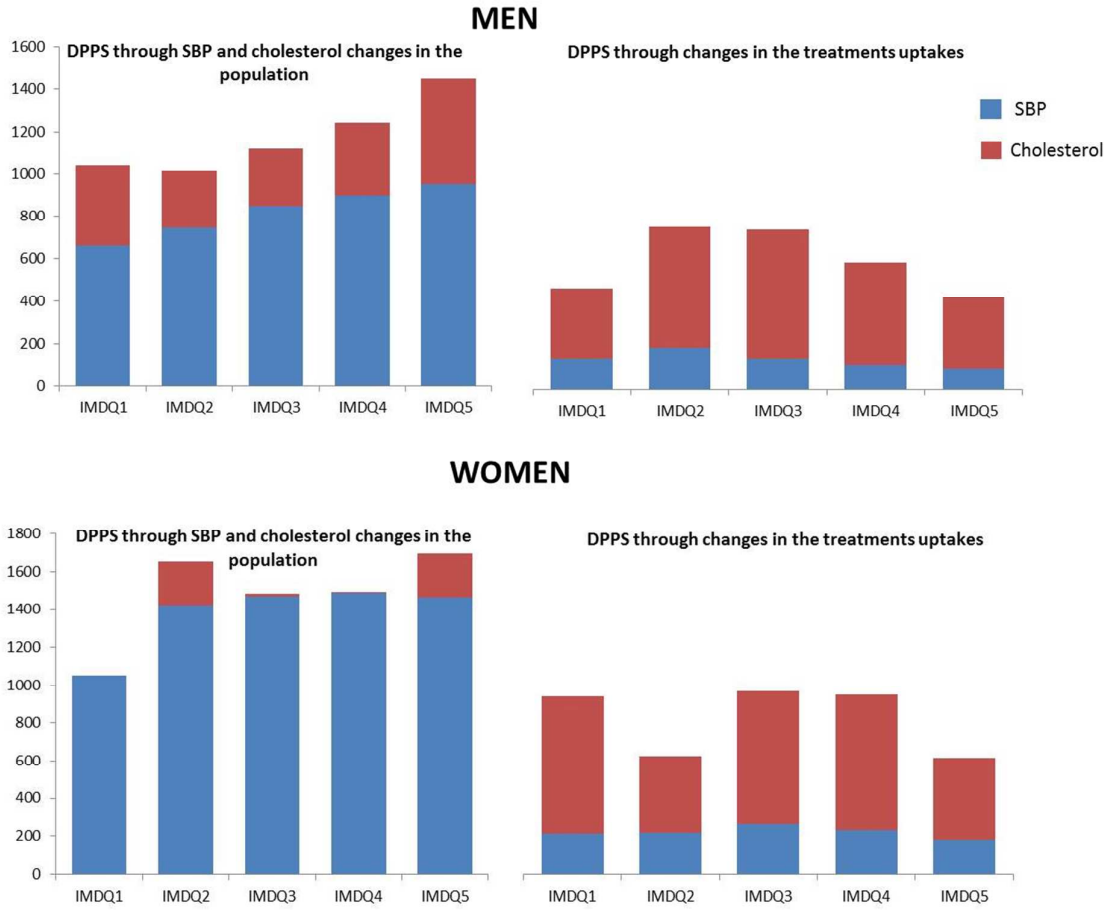
Gender differences

Figures 4 shows the number of deaths prevented or postponed in men and women, from falls in the population mean levels of SBP and cholesterol (Figure 4a, left panels) and from increases in the treatment uptakes levels (Figure 4b, right panels). For men, although most of the mortality reduction came from population falls in SBP, cholesterol reductions have also a considerable larger effect in

reducing mortality compared to women (four times higher). By contrast, the number of DPPs due to increases in treatment uptake in men appeared remarkably equitable across SES groups.

For women, the impressive reduction in SBP mean level between 2000 and 2007, contributed the most to the total mortality reduction and in all quintiles, whereas population level reductions of cholesterol had a smaller benefit. Moreover, the joint benefit of increasing treatment uptakes (antihypertensive and statins) in women appeared to have an important effect: for example, in the most affluent quintile (IMDQ1) the reduction in DPPs due to the increase in uptakes for women was almost as effective as the population-wide falls in both sexes for that quintile.

However, in terms of differences between men and women, the results of the uncertainty analysis suggest that these are not significant in statistical terms. More detailed outputs split by gender can be found in the section 5 of Technical Appendix.



Figures 4and 4b: Number of DPPs from changes in the population in SBP and cholesterol, changes in uptakes levels for anti-hypertension and dyslipidaemia between 2000 and 2007 in England, stratified by deprivation quintiles

Discussion

Coronary heart disease mortality in England fell by a remarkable 34% between 2000 and 2007. This represents an impressive 38,000 fewer deaths from CHD in 2007 than if the 2000 mortality rates had persisted. Reductions in major cardiovascular risk factors of blood pressure and cholesterol explained almost two thirds of this large mortality fall.

Blood pressure trends

Declines in the population blood pressure level made the largest contribution to the overall fall in CHD mortality. In contrast, anti-hypertension treatments produced only modest benefits. Firstly, because the baseline CHD event rate was low in asymptomatic individuals (≤ 1% per year) yielding only a small reduction of the attributable risk during the period of study (24). Secondly, treatment efficacy is low and thirdly blood pressure control is still poor (adherence levels to medication are around 60%) (8), leading in conjuction to a substantial residual risk (22, 24).

Cholesterol trends

Population-wide falls in cholesterol levels averted more deaths in the most deprived quintiles, reflecting similar absolute falls but much higher baseline mortality rates. The increase in the uptake of statins between 2000 and 2007 made an even greater contribution to the overall mortality fall: two fold greater than the change in population cholesterol (16% versus 6%), and with equitable benefits across all five SES groups.

Comparisons with other studies

Our results are consistent with previous analyses in the UK and around the world, supporting the importance of this study beyond England. Using the IMPACT model to examine contributions to the overall reductions in CHD mortality in England and Wales population between 1981 and 2000, Unal, Critchley (4) reported a higher contribution from blood pressure changes (compared to cholesterol). Some 76% of this contribution was attributable to population-wide changes rather than anti-hypertensive medications. IMPACT analyses carried out in the US and Irish populations between 1980-2000 and 1985-2000 likewise observed substantially greater benefits attributable to secular changes in risk factors rather than treatments (23, 25).

The analysis by DeWilde, Carey (26) suggested that reported blood pressure treatments were responsible only for the 25% of 5mmHg reduction in SBP during the period 1994-2009 for England.

Emberson et al Emberson, Whincup (27) applied a very different methodology using evidence from randomised control trials and cohort studies to analyse the effectiveness of population-wide changes in risk factor levels against the high risk individual approach. Their findings were entirely consistent

with ours. They concluded that a mere 10% reduction in population-wide blood pressure and cholesterol levels might achieve a 45% reduction in cardiac events in the long term. Whereas it would be need to provide treatment to approximately 26% of the UK population in high risk to achieve a only a 34% reduction in cardiac events. The US CHD policy model likewise reported that population-wide reductions of salt intake (3 g per day) might prevent between 44,000 and 90,000 deaths (28).

Strengths & limitations

This is the first IMPACT model to quantify the contributions of population risk factors and primary prevention treatments to recent changes in CHD mortality rates by socioeconomic quintiles.

The datasets used for the model are representative of the English population and used deprivation scores for area of residence as an acceptable proxy indicator for socioeconomic status. This allowed a sufficient sample size to quantify the effect of risk factor modification through changes in population-wide risk factor levels and treatment uptake.

Unlike, the previous IMPACT$_{SEC}$ models (Bajekal, Scholes (1) and Scholes, Bajekal (2)), our study stratifies the analysis and results by gender. This allowed us to gain valuable new insights, for example changes in SBP and cholesterol population levels for women led to the highest number of DPPs for all quintiles. More surprisingly, the change in uptake levels for women in the least deprived quintile was almost as effective as the population-wide changes in SBP and cholesterol. This all suggests that any attempt to tackle the socioeconomic inequalities in CHD mortality should explicitly consider these gender differences.

However, our study limitations should also be acknowledged. Firstly, the area-level categorisation may not be representative of individual circumstances. Furthermore, observed SES differences in CHD mortality might reflect not material deprivation but other confounding and mediator factors such as alcohol consumption, obesity or ethnicity. However, the IMD is a comprehensive multi-dimensional construct of socioeconomic status made up of seven domains, and based on small geographical areas (less than 1500 residents) called Lower Level Super Output Areas (LSOAs). The advantage of using LSOAs is that their smaller geographical sizes also allow for a more detailed knowledge of deprived areas.

Our risk factor effect data might still have some residual confounding. Statins and anti-hypertensive medication data is from surveys, therefore some misclassification bias might be present.

We assumed that treatments and lifestyle changes have an immediate effect on CHD mortality, which might not be entirely true. However, Capewell and O'Flaherty (29, 30) pointed out evidence from clinical trials and policy interventions which consistently suggests that changes in diet and lifestyle across entire populations can be rapidly followed by dramatic declines in mortality.

We assumed that changes in the risk factors and treatment uptakes have equal effect across socioeconomic groups. However, the benefits of falls in risk factors or increases in treatment uptakes may be higher in more affluent groups (1). This may partly explain the faster rates of CHD mortality decline in the most affluent quintiles as Bajekal, Scholes (11) pointed out. Likewise, we assumed that the relative risk reduction due to treatments remained constant from 2000 to 2007.

We simply subtracted the mortality gains from increasing uptake levels of statins from the overall gains due to reductions in total cholesterol to estimate the impact of population-wide reduction in total cholesterol due to non-pharmacological change only. This mutually exclusive adjudication of cause adjustment might overestimate medication benefit.

Given the background of higher mortality and morbidity in the more deprived quintiles, DPPs might overestimate the actual health gain, as we don't know the additional life span gained by preventing a specific death at a specific time. This might result in a lesser reduction in inequalities than DPPs alone would suggest.

Finally, our model was not able to explain around 14% of the total CHD mortality fall between 2000 and 2007. One possible contributor might be the exclusion of other "upstream" cardiovascular risk factors, which might affect SES groups differentially, for example, psychosocial stress (31).

Implications for public health and clinical care

This study shows that population-wide secular falls in blood pressure and cholesterol have substantially helped to decrease CHD mortality and reduce the associated socioeconomic disparities in absolute terms. Furthermore, as we discussed earlier, there is an increasing body of evidence to support the use of population-wide approaches to reduce CHD risk factors. Mackenbach, Lingsma (32) recently evaluated 22 successful preventive interventions in the Netherlands. Approximately 75% of the health gains during the period 1970-2010 were achieved by a population approach and just 25% by a high risk individual approach.

In the UK, the population-wide fall in blood pressure is consistent with the recent successful implementation of policies to reduce salt intake. Similar trends have been reported in other developed countries (22, 24). There are also several international examples where policy interventions have proven to be effective at achieving significant reductions in saturated fats, trans-fats and calories in processed foods and takeaway meals (28, 33-35). However policies to reduce saturated fats and trans-fats have thus far been neglected in the UK (36).

Conversely, targeting high-risk individuals with medication appears less effective and may also widen socioeconomic inequalities in CHD mortality (37,38). Any intervention that requires people to mobilise their own resources (material and psychological) will understandably favour those who have

greater resources (37) and thus widen social inequalities. Thus, those with the poorest health will benefit the least from such interventions (38).

However, there is no simple choice between either population-based or high risk strategies to reduce CHD mortality. The approaches are complementary in delivering the greatest public health benefit (39, 40). It is, however, clear that individual-based treatment strategies can afford only modest reductions in mortality compared with addressing risk factors population wide.

Severely limited health care budgets are now forcing planning systems to consider how best to allocate future resources. Our results strengthen the case for greater emphasis on preventive approaches, particularly population based policies to reduce blood pressure and cholesterol. Such strategies might be more powerful, rapid, cost-effective, and equitable than additional preventive medications (36).

Author contributions

MGC drafted the manuscript, analysed the results and conducted the uncertainty analysis in collaboration with S Capewell, M O'Flaherty and R. Ahmed. R. Ahmed conducted the initial literature review and initial set up of the model in collaboration with S Capewell. N Hawkins, S Scholes, E Wilkinson, J Lucy contributed to the interpretation of the results and to the drafting and finalisation of the manuscript

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

Data, $IMPACT_{SEC}$ spreadsheet and detailed results are available upon request by emailing Maria Guzman-Castillo.

Role of sponsor

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Transparency declaration

The lead author Maria Guzman Castillo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been reported.

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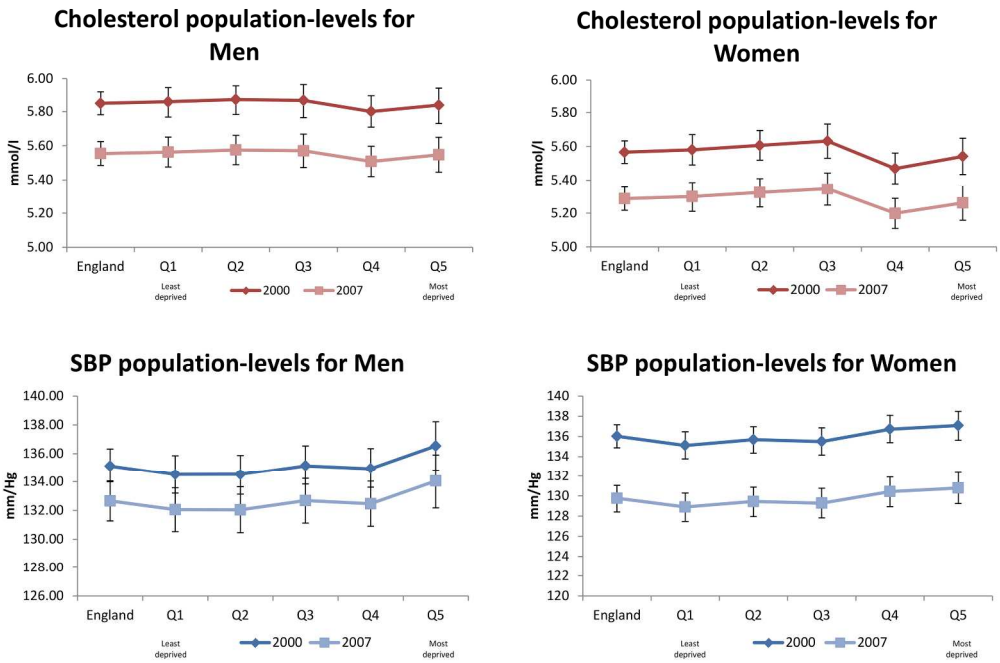

Mean values of SBP and cholesterol between 2000 and 2007 for England and stratified by deprivation quintiles and sex (95% UI)
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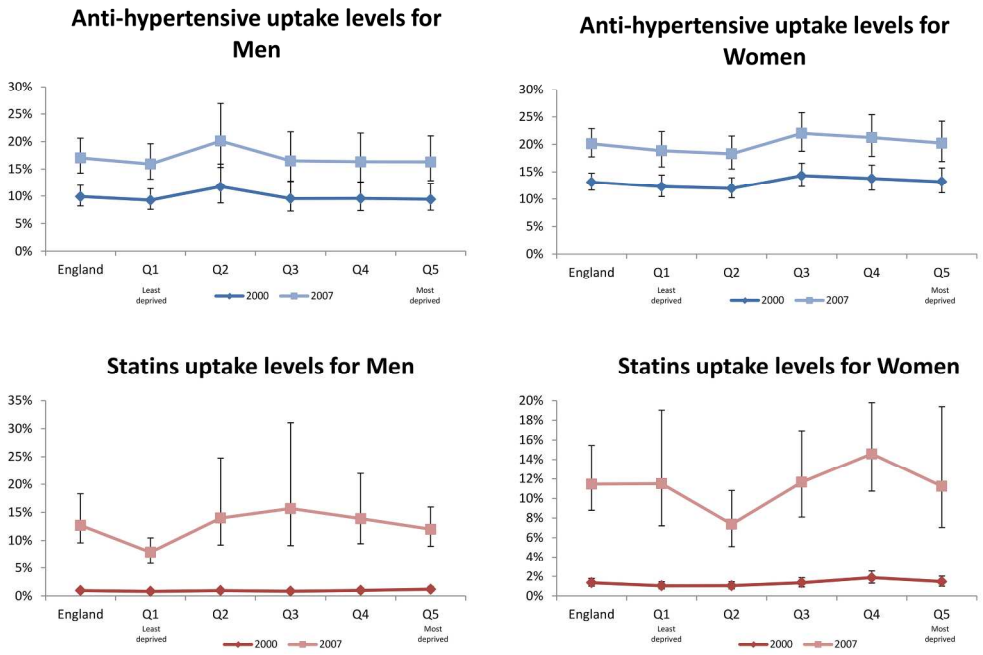
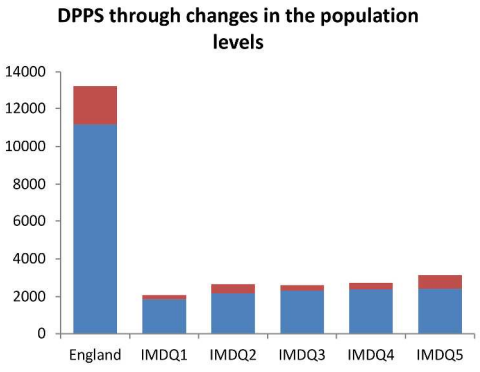
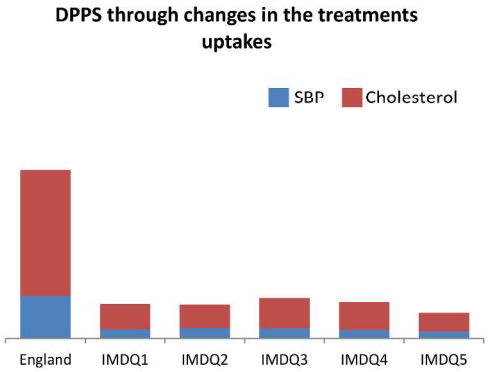


Uptake levels and proportion change in treatment uptake between 2000 and 2007 for England stratified by deprivation quintiles (95% UI)
113x74mm (600 x 600 DPI)

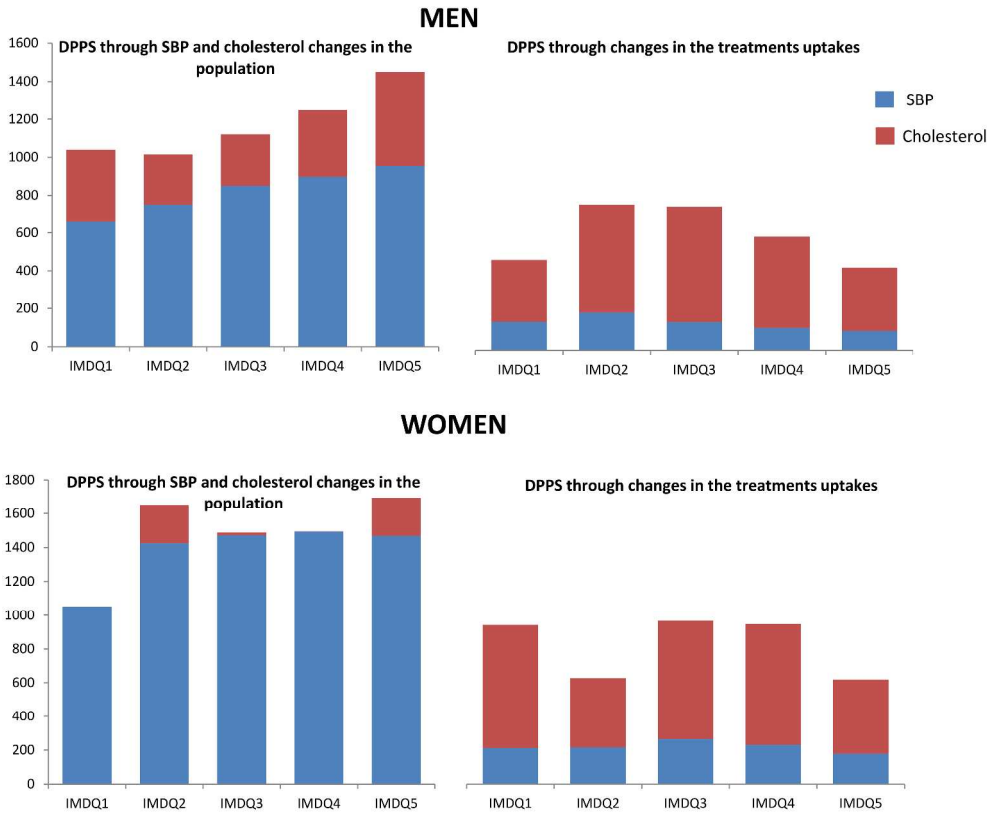




DPPs	England	IMD 1	IMD 2	IMD 3	IMD 4	IMD 5
Total	13253	2093	2666	2608	2742	3143
SBP	11162	1861	2168	2321	2391	2421
Cholesterol	2091	232	498	287	351	722

DPPs	England	IMD 1	IMD 2	IMD 3	IMD 4	IMD 5
Total	7098	1411	1386	1713	1539	1049
SBP	1798	357	411	408	345	277
Cholesterol	5300	1054	975	1305	1194	772

Number of deaths prevented or postponed (DPPs) between 2000 and 2007 in England attributable to changes in the population in SBP and cholesterol (Fig 3a, left panel), changes in uptakes levels for anti-hypertensive treatments and statins (Fig 3b, right panel); stratified by deprivation quintiles



Number of DPPs from changes in the population in SBP and cholesterol, changes in uptakes levels for anti-hypertension and dyslipidaemia between 2000 and 2007 in England, stratified by deprivation quintiles

TECHNICAL APPENDIX FOR THE IMPACT$_{SEC}$ MODEL

Contents

1 Overview of the IMPACT$_{SEC}$ model

The IMPACT model accommodates sub-national variation in CHD mortality trends by socioeconomic circumstances (IMPACT$_{SEC}$ model). We used the Index of Multiple Deprivation 2007 (IMD) quintiles as a proxy indicator of socioeconomic circumstances. This model examines the effects of changes in treatment uptake and risk factor trends on changes in mortality from coronary heart disease (CHD) among adults in England aged 25 years and over, stratified into equal quintiles by population size. The tables included in this Technical Appendix provide details about the sources and methods that were used.

2 METHOD AND EXAMPLES OF DEATHS PREVENTED OR POSTPONED (DPP) CALCULATIONS

2.1. Changes in mortality rates from CHD, England 2000 to 2007

Data sources used in examining the changes in CHD mortality rates over 2000 to 2007 are shown in Table A. Mortality rates from CHD were calculated using the underlying cause of death (*2000*: ICD9 410-414; *2007*: ICD10 I20-I25). Both unadjusted and age-adjusted mortality rates were calculated. The direct method of age-standardisation was used with the European Union reference population as standard.

2.2. Expected and observed number of deaths from CHD

Data sources used to estimate the observed and expected number of deaths from CHD for 2000 and 2007 are shown in Table A. The expected number of CHD deaths in 2007 was calculated by multiplying the age-sex-IMD quintile specific mortality rates from CHD in 2000 by the population counts for 2007 in that age-sex-IMD quintile stratum. Summing over all strata then yielded the expected number of deaths in 2007 had mortality rates remained unchanged. The difference between the number of expected and observed deaths from CHD represented the mortality fall, or the total DPPs in 2007 relative to 2000. Population counts, CHD mortality rates, observed and expected numbers of deaths are shown in sections 3.1and 3.2

2.3. Treatment component of IMPACT$_{SEC}$ model

The treatment component of the IMPACT$_{SEC}$ model included nine mutually exclusive CHD patient groups (see below). However, **for the purposes of our model, we just take into account groups 8 and 9**

1. Patients treated in hospital for acute myocardial infarction (ST-elevation myocardial infarction and non-ST elevation acute coronary syndrome)
2. Patients admitted to hospital with unstable angina
3. Community-dwelling patients who have survived a myocardial infarction for over a year
4. Patients who have undergone a revascularisation procedure up to and including the years 2000 and 2007: Coronary Artery Bypass Grafting (CABG), or a Percutaneous Coronary Intervention (PCI)
5. Community-dwelling patients with stable coronary artery disease
6. Patients admitted to hospital with heart failure (due to CHD)
7. Community-dwelling patients with heart failure (due to CHD)
8. **Hypercholesterolaemic subjects without CHD eligible for cholesterol lowering therapy such as statins**
9. **Hypertensive individuals without CHD eligible for anti-hypertensive therapy**

The general approach to calculating the number of DPPs from an intervention among a particular patient group was first to stratify by age, sex and IMD quintile; then to multiply the estimated number of patients in 2007 in turn by: the proportion of these patients receiving a particular treatment; the one-year case fatality rate; and the relative reduction in the case fatality rate due to the administered treatment. Sources for treatment uptake are shown in sections 3.3 and 3.4. Sources for estimates of treatment efficacy (relative risk reductions) are shown in section 3.5 . We obtained the relative risks based on the most recent published systematic reviews and meta-analyses of epidemiological studies. Each treatment relative risk value in the model was based on a meta-analysis comparison with an older therapy, or in some cases with a placebo if relevant. Age-sex specific case fatality rates for each patient group are presented in section 3.6

It was assumed that compliance (adherence), i.e. the proportion of treated patients actually taking therapeutically effective levels of medication, was 100% among hospital patients, 70% among symptomatic community patients, and 50% among asymptomatic community patients taking lipid-lowering drugs or anti-hypertensive medication for primary prevention. An adjustment was also made in certain cases for sub-optimal dose.

Example 1: Estimation of DPPs from a specific treatment

Mortality fall as a result of taking statins in men aged 55-64 in the most affluent quintile

For example, in 2007, about 685,000 men aged 55-64 were classified as the most affluent quintile. Uptake of statins in primary prevention was estimated to be approximately 15% with 100% assumed to comply. Statins in primary prevention reduces case fatality in patients by approximately 35%. The underlying one-year case fatality rate in these men was approximately 0.6%. The DPPs for at least a year were therefore calculated as:

Patient numbers* × *treatment uptake* × *compliance* × *relative mortality reduction* × *one year case fatality

= 685,000× 15% × 50% × 35% × 0.6% ≈ 108 DPPs

This calculation was then repeated for each age-sex-IMD quintile group.

2.4. Risk factor component of IMPACT$_{SEC}$ model

The second part of the IMPACT$_{SEC}$ model estimated the number of DPPs related to changes in cardiovascular risk factor levels in the population. The risk factors considered were total cholesterol and systolic blood pressure. The Health Survey for England was used to calculate trends in the prevalence (or mean values) of each risk factor (section 3.7). For the purposes of this paper, we used the regression approach to calculate DPPs from changes in risk factors.

In this approach regression approach the number of CHD deaths in 2000 (the start year) after adjusting for population change between 2000 and 2007 were multiplied by the absolute change in risk factor level, and by a regression coefficient ('beta') quantifying the estimated relative change in CHD mortality that would result from a one-unit change in risk factor level (see section 3.9). Natural logarithms were used, as is conventional, in order to best describe the log-linear relationship between absolute changes in risk factor levels and relative change in mortality. Levels of risk factors in 2000 and 2007 by sex and IMD quintile are shown in section 3.8.

Example 2: Estimation of DPPs from risk factor changes using regression method

Mortality fall due to reduction in SBP in women aged 55-64 in the most affluent quintile

For example, in 2000, there were 227 CHD deaths among 573,291 women aged 55-64 years in the most affluent quintile. The population total had increased to 714,111 in 2007. Applying the CHD death rate from 2000 (39.6 per 100,000) to the 2007 population gives an (adjusted) total of 283 expected deaths in 2007.

Mean SBP in this group fell by an estimated 4.28 millimetres of mercury (mmHg) (from 133.8 in 2000 to 129.5 in 2007). The largest meta-analysis reports an estimated age-sex specific reduction in mortality of 50% for every 20 mmHg reduction in SBP, generating a logarithmic coefficient of -0.035 (i.e. natural logarithm of 0.5 divided by 20). The subsequent reduction in CHD deaths between 2000 and 2007 was then estimated as the product of three variables:

DPPs = expected CHD deaths in 2007 (had mortality rates in 2000 remained constant) × absolute risk factor reduction between 2000 and 2007 × regression coefficient exponentiated

DPPs = (1-(exponential (regression coefficient × absolute change))) × expected deaths in 2007

DPPs = (1-(exponential (-0.035 × 4.28))) × 283 ≈ 39

This calculation was then repeated for each age-sex-quintile group.

The regression coefficients were assumed equal across deprivation quintiles. A 'fixed gradient' approach was used to stabilise estimates of risk factor change across the quintiles; this method is discussed in 2.5.5

2.5. Cumulative risk-reduction

2.5.1. Background

CHD deaths are usually caused by multiple risk factors acting simultaneously. Hence, part of the effect of one risk factor may be mediated through another. For example, physical inactivity may have a direct effect on CHD but may also partly be mediated through its effects on BMI and blood pressure. It is recommended therefore that mortality benefits attributable to risk factors which may be causally related, or which overlap in population groups, should not be combined by simple addition. Ideally, their effects should instead be jointly estimated [12-16].

We do not currently have sources that allow joint estimation of relative risks for combinations of risk factors in this English population. However, several large cohort studies and meta-analyses have published independent risk reduction coefficients for each risk factor included in this study. One approach commonly used is to calculate the **cumulative risk**-reduction [17]. This approach accounts for risk factor prevalence overlap but assumes independence of effects [14-15]. The general equation for cumulative risk-reduction is stated as:

Combined (or cumulative) effect (CR) =

$$1 - ((1-a) \times (1-b) \times (1-c) \times \ldots \times (1-n)) \quad \textbf{[1]}$$

Thus for CHD risk factors, the specific equation is stated as:

$$\textbf{CR} = 1 - ((1-R_{SBP}) \times (1-R_{smoke}) \times (1-R_{diabetes}) \times \ldots \times (1-R_n))$$

where R denotes the mortality change attributable to a specific risk factor.

This is in contrast to additive risk-reduction (AR):

$$\textbf{AR} = (R_{SBP}) + (R_{smoke}) + (R_{diabetes}) + \ldots + (R_n) \quad \textbf{[2]}$$

2.5.2. 1.3.2 Implementation

For the purposes of this modelling study we first calculated the (additive) DPPs attributed to risk factor change. These were then adjusted down by using the ratio:

Adjustment factor = CR/AR

The adjustment factor would always be expected to be less than 1. In other words, cumulative risk factor reduction would be smaller than the mortality benefits arrived at by a simple summation of the benefits of each risk factor in turn.

The proportional change in the CHD mortality rate between two time points (denoted by R) was calculated using the following formulas [14-15]:

Continuous risk factors:

$R_{continuous} = 1 - \exp(\text{beta} \times \text{absolute mean risk factor change})$ **[3]**

and P denotes prevalence at the start-year; RR the relative risk in CHD mortality associated with risk factor presence; and ΔP the change in prevalence between the start and final years.

Formulas [3] and [4] were used to calculate the proportional change in the CHD mortality rate (R) for each risk factor and the steps involved in their estimation are detailed below. However, we made two modifications to the methodology used in previous work [14-15]. First, we estimated aggregate change over a seven year period (2000-2007) rather than average annual change. Second, additive and cumulative risk-reduction was calculated by using the **absolute** values of R (i.e. disregarding the direction of risk factor change). These are discussed in turn below.

2.5.3. Calculating aggregate change in risk factors over 2000 and 2007

Previous studies [14-15] estimating cumulative risk factor reduction calculated the average annual percentage change in CHD mortality attributable to annual falls in levels of smoking, blood pressure and cholesterol (where annual falls in CHD mortality and risk factor levels were estimated over a specified number of years). Rather than estimate the average annual change over a specific range of years, we were interested in calculating the R values between two fixed points in time (start and end years of the model), seven years apart, 2000 and 2007. We therefore adapted formulas [3] and [4], substituting change over the seven year study period for the estimation of annual average change. We checked our resulting estimates of cumulative risk reduction calculated over seven years against uprating the annual average by a factor of seven. The two sets of estimates were found to be virtually identical.

2.5.4. Regression models to estimate risk factor change, 2000-2007

Formula [3] requires estimates of absolute and relative change in risk factors, respectively. Regression modelling was used to estimate the magnitude of absolute and relative change. In order to smooth fluctuations in Health Survey for England data, we obtained estimates of risk factor change for each risk factor over 2000-2007 by using the predicted values from regression models. Separate models were fitted by sex and seven ten-year age-bands.

The dependent variable was the risk-factor level for each survey respondent; calendar year (i.e. year of interview) was the explanatory variable entered in the model as a continuous term.

Absolute change was measured as the difference between the predicted values for 2000 and 2007, by age and sex.

Estimates of risk factor change were not calculated separately by deprivation quintile owing to small sample sizes, especially in those risk factors covered by the survey in intermittent years. Data since 2003 were weighted for non-response at each stage of data collection. Although it was just beyond the time period covered by the $IMPACT_{SEC}$ model, the most recent survey data available (2008) was included in fitting the regressions to improve estimation of the underlying change. Analyses were conducted using Stata Version 11.1.

2.5.5. Adjustment factors by age-sex-IMD

The adjustment factors (section 3.10) fell within the range of 0.83 to 0.96. The largest adjustment (0.83) was applied to the DPPs for women aged 65-74 resident in the most deprived areas (IMDQ5). The adjustment factors for the deprivation quintiles were, on average, ± 0.01 of the overall adjustment ratio for England across the 14 age and sex groups. The adjustments were on average, slightly higher for women (0.89) than men (0.92); and were higher in IMDQ5 than in IMDQ1 (mean values 0.8924 and 0.9089, respectively). Hence the adjustment values indicated a larger downward adjustment to the additive DPPs in the most deprived areas relative to the most affluent.

2.6. Overlap between pharmacological and non-pharmacological contributions to risk factor DPPs

Risk factor improvements, such as lower blood pressure or lower total cholesterol, may be achieved through medications, lifestyle changes, or a combination. In order to separate the DPPs from pharmacological versus non-pharmacological contributions to CHD mortality, we subtracted the DPPs calculated in the treatment (primary prevention) component of the model from the DPPs calculated in the risk factor component. That is, to estimate the impact of population-wide reduction in total cholesterol due to non-pharmacological change, we subtracted the estimated effect of statins for the primary prevention of CHD from the overall number of DPPs due to change in mean total cholesterol. Similarly, to estimate the impact of the population-wide reduction in SBP we subtracted the estimated effect of anti-hypertensive medication for primary prevention from the overall number of DPPs due to change in mean SBP levels.

2.7. Net effects

As all treatments were in use in 2000, the net benefit of an intervention in 2007 was calculated by subtracting the expected number of deaths prevented if the uptake rates in 2000 remained constant from the estimated number of deaths prevented calculated using the 2007 uptake rates. This is illustrated in the example below.

Example 5: Net effects for treatments

For example, in 2007, about 685,000 men aged 55-64 were classified as the most affluent quintile. Uptake of statins in primary prevention was estimated to be approximately 15% with 50% assumed to comply. Statins in primary prevention reduces case fatality in patients by approximately 35%. The underlying one-year case fatality rate in these men was approximately 0.6%. The DPPs for at least a year were therefore calculated as:

Patient numbers × treatment uptake × compliance × relative mortality reduction × one year case fatality

$= 685{,}000 \times 15\% \times 50\% \times 35\% \times 0.6\% \approx 108$ *DPPs*

Applying the uptake rate in 2000 (2.7%) gave a total of 19 DPPs:

The net DPPs were therefore:

$$\textit{Net DPPs} = \textit{DPPs using uptake}_{2007} - \textit{DPPs using uptake}_{2000}$$

$= 108 - 19 = 89$

The estimated changes in treatment uptake between 2000 and 2007 by deprivation quintile are shown in Table H.

2.8. Uncertainty analyses

We implemented uncertainty analysis in Excel using Ersatz (version 1.0 available at http://www.epigear.com). This is an add-on which allows probabilistic bootstrapping in Excel. Ersatz allows repeated random draws from specified distributions for input variables and then calculates the 95% uncertainty intervals from the realised values of the output variable (deaths prevented or postponed). For the $IMPACT_{SEC}$ model, we calculated the uncertainty intervals based on 1000 draws – taking the 95% uncertainty intervals from the 2.5^{th} and 97.5^{th} percentiles. The parameter distributions used for the input variables to the DPP calculations are shown in Table M. Worked examples using Ersatz are shown below Table M.

2.8.1. Allocating areas to socioeconomic quintiles using the Index of Multiple Deprivation, 2007

The Index of Multiple Deprivation (IMD) is a composite index of relative deprivation at small area level based on seven domains: income; employment; health deprivation and disability; education, skills and training; barriers to housing and services; crime and disorder; and living environment [19]. The IMD 2007 score of all small areas in England (average population 1,500) were ranked in ascending order and grouped into equal quintiles (about 6,500 areas in each), with quintile one (IMDQ1) including the most affluent and quintile five (IMDQ5) the most deprived areas. Based on their postcode of residence, patients treated in hospital (e.g. recorded in Hospital Episode Statistics) or in the community (e.g. in the General Practice Research Database) were matched via their area of residence to the corresponding deprivation quintile by the data providers to protect patient anonymity. Mortality counts were similarly aggregated into deprivation quintiles by the Office for National Statistics before being released to us for research purposes.

As the IMD 2007 includes rates of premature total mortality in the health deprivation and disability domain, its use to quantify health inequalities risks a tautology. However UK studies have shown that removing the health domain had little effect on either the assignment of areas into their deprivation quintile or the relationship between area-based deprivation and health [20].

Conceptually, the IMD 2007 is a measure of deprivation, not a measure of affluence. Hence, areas with the lowest scores are not necessarily the most affluent; rather they have the lowest concentration of deprived people. In this paper for clarity and to easily distinguish between the extreme ends of the deprivation spectrum, we have used the term ‘most affluent’ and ‘most deprived’ rather than ‘least deprived’ and ‘most deprived’.

3 Data sources

3.1. Population and patient data sources used in the IMPACTSEC model

Information	Source
Population data	
Population counts and CHD deaths stratified by age, sex, and Index of Multiple Deprivation quintiles	Office for National Statistics (ONS): (*2000*: ICD9 410-414) (*2007*: ICD10 I20-I25)
Patients eligible for primary prevention therapies:	
Lipid-lowering drugs	Prevalence of never having had angina or heart attack and currently taking lipid lowering drugs prescribed by a doctor from the Health Survey for England (HSfE 1998, 2003, and 2006) (http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles-related-surveys/health-survey-for-england)
Hypertension treatment	Prevalence of never having had angina or heart attack and currently taking medication specifically prescribed to treat high blood pressure from the Health Survey for England (HSfE 1998, 2003, and 2006)

Table A: Population and patient data sources used in the IMPACTSEC model

3.2. Demographic data 2000 and 2007 by sex and deprivation quintiles

	Year	England	IMDQ1	IMDQ2	IMDQ3	IMDQ4	IMDQ5
Male							
Population (000s)	**2000**	16242	3353	3372	3321	3186	3011
	2007	17002	3525	3542	3486	3335	3114
Observed CHD deaths	**2000**	56713	9146	10868	11671	12094	12934
	2007	41713	6962	8129	8535	8723	9364
Age-standardised rate (00,000)	**2000**	310	238	270	301	349	415
	2007	200	147	170	191	231	294
Annual % fall†		6.0	6.6	6.4	6.3	5.7	4.8
Expected deaths††	**2007**	63685	11207	12856	13348	13098	13176
Target DPPs‡	**2007**	21972	4245	4727	4813	4375	3812
% of expected deaths prevented	**2007**	34.5	37.9	36.8	36.1	33.4	28.9
Female							
Population (000s)	**2000**	17710	3618	3663	3618	3493	3318
	2007	18279	3803	3820	3747	3571	3337
Observed CHD deaths	**2000**	46530	7383	8959	9789	10093	10306
	2007	32461	5350	6315	6812	6953	7031
Age-standardised rate (00,000)	**2000**	148	115	128	143	164	198
	2007	94	70	79	90	107	136
Annual % fall†		6.3	6.7	6.7	6.4	5.9	5.2
Expected deaths††	**2007**	48559	8458	9812	10348	10162	9778
Target DPPs‡	**2007**	16098	3108	3497	3536	3209	2747
% of expected deaths prevented	**2007**	33.2	36.7	35.6	34.2	31.6	28.1
Total							
Population (000s)	**2000**	33952	6972	7035	6939	6678	6329
	2007	35281	7328	7363	7233	6906	6451
Observed CHD deaths	**2000**	103243	16529	19827	21460	22187	23240
	2007	74174	12312	14444	15347	15676	16395
Age-standardised rate (00,000)	**2000**	229	177	199	222	257	306
	2007	147	109	124	141	169	215
Annual % fall†		6.1	6.7	6.5	6.3	5.8	4.9
Expected deaths††	**2007**	112244	19665	22669	23696	23260	22953
Total DPPs‡	**2007**	38070	7353	8225	8349	7584	6558
% of expected deaths prevented	**2007**	33.9	37.4	36.3	35.2	32.6	28.6

Table B: Demographic data 2000 and 2007 by sex and deprivation quintiles

† **Annual % fall = (1-(2007 rate/2000 rate)^(1/7))**

†† **Expected deaths = CHD deaths expected in 2007 had 2000 CHD rates remained.**

‡ **DPPs, deaths prevented or postponed. DPPs = expected – observed deaths in 2007**

3.3. Data sources for treatment uptake levels

Primary prevention therapies:	
Lipid-lowering drugs	Prevalence of never having had angina or heart attack and currently taking lipid lowering drugs prescribed by a doctor from the Health Survey for England (HSfE 1998, 2003, and 2006).
Anti-hypertensive medication	Prevalence of never having had angina or heart attack and currently taking medication specifically prescribed to treat high blood pressure from the Health Survey for England (HSfE 1998, 2003, and 2006).

Table C: Data sources for treatment uptake levels

3.4. Treatment uptake in 2000 and 2007

	England			IMDQ1			IMDQ2			IMDQ3			IMDQ4			IMDQ5		
	N	Uptake (%)		N	Uptake (%)		N	Uptake (%)		N	Uptake (%)		N	Uptake (%)		N	Uptake (%)	
		2000	2007		2000	2007		2000	2007		2000	2007		2000	2007		2000	2007
Anti-hypertension	35,280,843	8.3	13.5	7,328,217	8.3	14.0	7,362,561	8.2	13.8	7,232,779	8.6	13.9	6,905,987	8.2	13.0	6,451,299	8.3	12.7
Statins	35,280,843	1.1	9.0	7,328,217	1.0	7.9	7,362,561	1.1	8.5	7,232,779	1.1	9.1	6,905,987	1.4	10.3	6,451,299	1.3	9.1

Table D: Treatment uptake in 2000 and 2007

†† We assumed no change in community-based CPR between 2000 and 2007

3.5. Clinical efficacy of interventions: relative risk reductions obtained from meta-analyses, and randomised clinical trials

Treatments	Relative risk reduction†	Comments	Source paper: First author (year), notes
Primary prevention therapies:			
Treatments for high blood pressure	13% (95% CI: 6,19)	OR=0.87 (95% CI: 0.81,0.94); RRR=13% (95% CI: 6,19) in those with high blood pressure without disease at entry. [RRR=29% (95% CI: 17,37) those with average blood pressure and CHD, treated with ACE inhibitors]	Law (2003) [51]
Statins	35% (95% CI: 11,52)	OR=0.65 (95% CI: 0.48,0.89); RRR=35% (95% CI: 11,52) for CHD mortality (only trials using statins), Figure 3 on page 4	Pignone (2000) [52]

Table E; Relatives risk reductions used in the model

†**Relative risk reduction (RRR) calculated as 1 – odds ratio**

3.6. Case fatality rates for each patient group

Patient group	Hypertension		Statins	
	Men	**Women**	**Men**	**Women**
25-34	0.000	0.000	0.000	0.000
35-44	0.001	0.001	0.001	0.001
45-54	0.002	0.002	0.002	0.002
55-64	0.006	0.004	0.006	0.004
65-74	0.014	0.014	0.014	0.014
75-84	0.035	0.035	0.035	0.035
85+	0.094	0.094	0.094	0.094

Table F: Case-fatality rates. Source Wijeysundera et.al (2010) [5]

3.7. Risk factors: variable definitions and source

The Health Survey for England (HSfE), an annual nationwide household survey of the English population, has been described in detail elsewhere [24]. Briefly, members of a stratified random sample (drawn from the Postcode Address File) that is socio-demographically representative of the English population were invited to participate. The annual household response rate was 75% in 2000, falling steadily to 66% in 2007. Data were collected at two visits: an interviewer's visit, during which a questionnaire was administered, followed by a visit from a trained nurse for all those interviewed who agreed. The nurse visit, which did not take place in 2004 among the general population sample, includes measurements and collection of blood, as well as additional questioning including use of prescribed medication (1998, 2003, and 2006).

Risk factor	HSfE survey years	Description
SBP (mmHg)	All years between 2000-7 except 2004	Calculated as the mean of the 2nd and 3rd readings for those who had not eaten, consumed alcohol or smoked in the 30 minutes prior to measurement. Those reporting taking blood pressure lowering drugs were included
Total cholesterol (mmol/l)	1998,2003,2006	Those reporting taking lipid lowering drugs were included

Table G: Definition of risk fators

3.8. Risk factor levels in 2000 and 2007 by sex and deprivation quintiles

The annual sample size of the Health Survey for England (HSE), roughly 14,000 adults aged 16 years and over, was not large enough to provide accurate and precise estimates of risk factor levels, and hence rates of change over time by age, sex, and deprivation quintiles. We considered a 'fixed gradient approach' for estimating risk factors changes.

The fixed gradient approach is based on the assumption that changes in pace and direction for each deprivation quintile were similar and therefore, most accurately measured by the overall national rates of change (across all age-sex groups). If this assumption holds, then relatively stable and plausible estimates for each quintile could be derived by scaling the national age-sex risk factor levels up or down using a fixed ratio/gradient.

The fixed gradient was derived by pooling together survey data for all available years from 2000 to 2007 to calculate risk factor estimates by age, sex, and deprivation quintiles. Then the pooled national estimate for 14 age-by-sex groups was set notionally to one, and the corresponding estimates for each deprivation quintile re-indexed to be below or above one (i.e. expressing the ratio of the deprivation quintile to national estimate). These index rates were then applied to the single year national estimates to derive the corresponding risk factor levels for that year. The fixed gradient was applied to both the start and end years of the model. The next table shows the risk factor levels in 2000 and 2007 by gender and deprivation quintiles using this approach.

	England		**IMDQ1**		**IMDQ2**		**IMDQ3**		**IMDQ4**		**IMDQ5**	
	2000	**2007**	**2000**	**2007**	**2000**	**2007**	**2000**	**2007**	**2000**	**2007**	**2000**	**2007**
Systolic blood pressure, mmHg												
Male	133.1	130.6	133.1	130.5	133.4	130.8	133.3	130.7	133.0	130.6	133.0	130.6
Female	131.0	125.6	130.7	125.3	131.6	126.6	131.2	125.7	131.1	125.6	130.6	125.1
Cholesterol, mmol/L												
Male	5.6	5.4	5.6	5.4	5.6	5.5	5.6	5.4	5.5	5.4	5.5	5.4
Female	5.7	5.5	5.7	5.6	5.8	5.6	5.7	5.5	5.6	5.4	5.6	5.5

Table H: Risk factor levels in 2000 and 2007

3.9. Beta coefficients for risk factors

Estimated β coefficients from multiple regression analyses for the relationship between absolute changes in population mean risk factors and percentage changes in coronary heart disease mortality for men and women, stratified by age. Data sources, values and comments.

Systolic blood pressure	**Age group (years)**				
	25-44	**45-54**	**55-64**	**65-74**	**75+**
Men (hazard ratio per 20 mmHg)	0.49	0.49	0.52	0.58	0.65
Men (log hazard ratio per 1 mmHg)	**-0.036**	**-0.035**	**-0.032**	**-0.027**	**-0.021**
Minimum	*-0.029*	*-0.028*	*-0.026*	*-0.022*	*-0.017*
Maximum	*-0.043*	*-0.042*	*-0.039*	*-0.032*	*-0.025*
Women (hazard ratio per 20 mmHg)	0.40	0.40	0.49	0.52	0.59
Women (log hazard ratio per 1 mmHg)	**-0.046**	**-0.046**	**-0.035**	**-0.032**	**-0.026**
Minimum	*-0.037*	*-0.037*	*-0.028*	*-0.026*	*-0.021*
Maximum	*-0.055*	*-0.055*	*-0.042*	*-0.039*	*-0.031*

Source: Prospective studies collaborative meta-analysis, Lancet 2002 [53]
Units: Percentage change in CHD mortality per 20 mmHg change in systolic blood pressure

Strengths: Large dataset, includes US data, adjusted for regression dilution bias, consistent with randomised controlled trials, results stratified by age and sex, with 95% confidence intervals

Limitations: Some publication bias still possible

Table I: Beta coefficients for SBP.

† **Risk reduction = 1 – hazard ratio**

Cholesterol	Age groups (years)					
	25-44	45-54	55-64	65-74	75-84	85+
Mortality reduction per 1 mmol/l						
Men	0.55	0.53	0.36	0.21	0.21	0.21
Women	0.57	0.52	0.35	0.23	0.23	0.23
Log coefficient						
Men	**-0.799**	**-0.755**	**-0.446**	**-0.236**	**-0.117**	**-0.083**
Minimum	*-0.639*	*-0.604*	*-0.357*	*-0.189*	*-0.093*	*-0.067*
Maximum	*-0.958*	*-0.906*	*-0.536*	*-0.283*	*-0.140*	*-0.100*
Women	**-0.844**	**-0.734**	**-0.431**	**-0.261**	**-0.174**	**-0.051**
Minimum	*-0.675*	*-0.587*	*-0.345*	*-0.209*	*-0.139*	*-0.041*
Maximum	*-1.013*	*-0.881*	*-0.517*	*-0.314*	*-0.209*	*-0.062*

Source: Prospective studies collaborative meta-analysis, Lancet 2007 [54]

Units: Percentage change in CHD mortality per 1 mmol/l change in total cholesterol

Strengths: Includes US data, adjusted for regression dilution bias, includes randomised controlled trials, RCT values consistent with observational data, results stratified by age and sex, with 95% confidence intervals

Limitations: Some publication bias still possible

Table J: Beta coefficients for cholesterol

† **Risk reduction = 1 – hazard ratio**

3.10. Cumulative benefit: Adjustment factors by age, sex and IMD quintile

In Section 1.2 we described how we adjusted down the DPPs calculated in an additive fashion over the risk factors by using the ratio of cumulative to additive risk-reduction. The 70 age-sex-IMD specific adjustment factors are shown below.

	Deprivation quintile					
	IMDQ1	**IMDQ2**	**IMDQ3**	**IMDQ4**	**IMDQ5**	**England**
			Men			
25-34	0.9464	0.9449	0.9463	0.9462	0.9434	0.9453
35-44	0.9196	0.9169	0.9179	0.9126	0.9110	0.9153
45-54	0.9335	0.9278	0.9205	0.9193	0.9083	0.9219
55-64	0.8957	0.8957	0.8883	0.8851	0.8762	0.8886
65-74	0.8885	0.8843	0.8846	0.8817	0.8720	0.8827
75-84	0.9182	0.9146	0.9134	0.9214	0.9149	0.9162
85+	0.9561	0.9569	0.9525	0.9520	0.9582	0.9547
			Women			
25-34	0.8799	0.8872	0.8846	0.8787	0.8782	0.8809
35-44	0.9148	0.9119	0.9014	0.9034	0.8892	0.9038
45-54	0.9038	0.9013	0.8937	0.8777	0.8546	0.8865
55-64	0.8862	0.8896	0.8842	0.8703	0.8560	0.8780
65-74	0.8620	0.8569	0.8523	0.8363	0.8307	0.8479
75-84	0.8803	0.8869	0.8824	0.8778	0.8622	0.8779
85+	0.9394	0.9399	0.9409	0.9463	0.9386	0.9410
Overall	0.9089	0.9082	0.9045	0.9006	0.8924	0.9029

Table K: Adjustment factors by age, sex and IMD quintile

3.11. Uncertainty analysis: parameter distributions, functions and sources

Table M records the type of distribution and associated functions for each of the input variables in the $IMPACT_{SEC}$ model. We implemented stochastic uncertainty analysis in Excel using Ersatz (version 1.0 available at http://www.epigear.com), an add-in that allows probabilistic bootstrapping in Excel [62]. Ersatz allows repeated random draws from specified distributions for input variables that are used to recalculate iteratively the model. It then calculates the 95% uncertainty intervals from the realised values of the output variable (deaths prevented or postponed). For the $IMPACT_{SEC}$ model, we calculated the uncertainty intervals based on 1000 draws taking the 95% uncertainty intervals as the 2.5^{th} and 97.5^{th} percentiles. Input variables taken from external sources (e.g. case fatality rates, beta coefficients and relative risk reductions) were randomly drawn from specified distributions but assumed constant across deprivation quintiles.

Input parameters	***Type of distribution and functions (Mean, Standard error)***	Source
Population		
Population counts and CHD deaths stratified by age, sex, and Index of Multiple Deprivation quintiles	• Population counts (no error) • Deaths expected in 2007 had CHD mortality rates in 2000 persisted (***Poisson distribution***)	Office for National Statistics
Risk factors		
Prevalence/mean estimates (pooled data; national estimates for 2000 and 2007)	• Continuous variables (Body Mass Index, SBP, total cholesterol, fruit and vegetable consumption): (***Normal distribution***: mean, SE of mean)	Health Survey for England
Beta coefficient: **SBP**	***Normal distribution*** (mean, SE of mean): M < 45 (-0.036,0.004); M 45-54 (-0.035,0.004) M 55-64 (-0.032,0.003); M 65-74 (-0.027,0.003) M 75-84 (-0.021,0.002); M 85+ (-0.016,0.002) F < 55 (-0.046, 0.005); F 55-64 (-0.035,0.004) F 65-74 (-0.032,0.003); F 75-84 (-0.026,0.003)	Prospective studies collaborative meta-analysis (2002) [53]. Parameters on the log scale.

	F 85+ (-0.019,0.002)	
Beta coefficient: **total cholesterol**	***Normal distribution*** (mean, SE of mean): M < 45 (-0.799,0.081); M 45-54 (-0.755,0.077) M 55-64 (-0.446,0.046); M 65-74 (-0.236,0.024) M 75-84 (-0.117,0.012); M 85+ (-0.083,0.009) F < 45 (-0.844,0.086); F 45-54 (-0.734,0.075) F 55-64 (-0.431,0.044); F 65-74 (-0.261,0.027) F 75-84 (-0.174,0.018); F 85+ (-0.051,0.005)	Prospective studies collaborative meta-analysis (2007) [54]. Parameters on the log-scale.
Aspirin Beta blockers ACE Inhibitors Statins Rehabilitation Warfarin	M & F (0.15,0.139) M & F (0.23,0.185) M & F (0.20,0.177) M & F (0.24,0.245) M & F (0.26,0.347) M & F (0.22,0.305)	ATC (2002) [35] Freemantle (1999) [29] Flather (2000) [40] Hulten (2006) [41] Taylor (2004) [43] Anand and Yusuf (1999) [42]
Primary prevention therapies: Statins		
Eligible patients: Population	Population counts (no error)	Office for National Statistics
Treatment uptake	% never having had angina or heart attack and currently taking lipid lowering drugs prescribed by a doctor: (***Beta distribution***: cases, sample-size minus cases)	Health Survey for England
Case fatality rate	Sample size (n) = never having had angina or heart attack and currently taking lipid lowering drugs in 2006: ***Beta distribution*** (cases = n × CFR estimate, non-cases = n – cases)	Wijeysundera et al (2010) [5]
Compliance	***Beta distribution*** (cases = n × assumed compliance, non-cases = n – cases)	Health Survey for England
Relative risk reduction: Statins	***Ersatz RR function*** (RRR, SE ln(RRR)): M & F (0.35,0.396)	Pignone (2000) [52]
Primary prevention therapies: Treatments for high blood pressure		
Eligible patients:	Population counts (no error)	Office for National Statistics

Population		
Treatment uptake	% never having had angina or heart attack and currently taking medication specifically prescribed to treat high blood pressure: (***Beta distribution***: cases, sample-size minus cases)	Health Survey for England
Case fatality rate	Sample size (n) = never having had angina or heart attack and currently taking medication to lower blood pressure in 2006: ***Beta distribution*** (cases = n × CFR estimate, non-cases = n – cases)	Wijeysundera et al (2010) [5]
Compliance	***Beta distribution*** (cases = n × assumed compliance, non-cases = n – cases)	Health Survey for England
Relative risk reduction: Treatments for high blood pressure	***Ersatz RR function*** (RRR, SE ln(RRR)): M & F (0.13,0.294)	Law (2003) [51]

Table L: Parameter distributions, functions and sources

4 Tables

DPPS through changes in the population						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	13253	2093	2666	2608	2742	3143
95% LL	8495	1187	1632	1577	1775	2302
95% UL	17371	2880	3551	3497	3590	3880
DPPS through changes in the treatments uptakes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	7098	1411	1386	1713	1539	1049
95% LL	3479	656	665	800	716	500
95% UL	14195	3069	2811	3819	3141	2135

Table M: CHD deaths prevented or postponed through changes in population and treatment uptakes between 2000 and 2007 in England, stratified by deprivation quintiles.

DPPS through SBP reduction						
Overall						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	12960	2218	2579	2729	2736	2698
95% LL	8181	1295	1537	1690	1776	1868
95% UL	17463	3086	3560	3723	3649	3468
Population wide changes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	11162	1861	2168	2321	2391	2421
95% LL	6500	978	1156	1322	1439	1612
95% UL	15093	2616	3024	3163	3190	3121
Anti-hypertension treatment						

	England	IMD quintile 1	IMD quintile 2	IMD quintile 3	IMD quintile 4	IMD quintile 5
		Affluent				Deprived
Mean	1798	357	411	408	345	277
95% LL	675	138	151	150	126	105
95% UL	3860	784	907	898	780	606

Table N: CHD DPPs through medication and population changes in SBP between 2000 and 2007 in England, stratified by deprivation quintiles

DPPS through Cholesterol reduction						
Overall						
	England	IMD quintile 1	IMD quintile 2	IMD quintile 3	IMD quintile 4	IMD quintile 5
		Affluent				Deprived
Mean	7391	1286	1473	1592	1545	1494
95% LL	3851	551	794	700	725	930
95% UL	14493	2900	2819	3669	3161	2579
Population wide changes						
	England	IMD quintile 1	IMD quintile 2	IMD quintile 3	IMD quintile 4	IMD quintile 5
		Affluent				Deprived
Mean	2091	232	498	287	351	722
95% LL	1020	43	282	56	129	496
95% UL	3148	419	709	516	572	944
Dyslipaedimia treatment						
	England	IMD quintile 1	IMD quintile 2	IMD quintile 3	IMD quintile 4	IMD quintile 5
		Affluent				Deprived
Mean	5300	1054	975	1305	1194	772
95% LL	2051	375	359	480	443	279
95% UL	12318	2679	2326	3369	2804	1869

Table O: CHD deaths prevented or postponed through medication and population changes in cholesterol between 2000 and 2007 in England, stratified by deprivation quintiles

5 Tables by gender

5.1. Men

DPPS through changes in the population						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	5872	1041	1015	1121	1247	1449
95% LL	3029	495	411	510	675	912
95% UL	8593	1557	1591	1709	1785	1960
DPPS through changes in the treatments uptakes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	3017	474	763	751	596	434
95% LL	1211	187	291	261	218	157
95% UL	7005	1017	1867	2144	1470	1028

Table P: CHD deaths prevented or postponed through medication and population changes in SBP and Cholesterol between 2000 and 2007 in England, stratified by deprivation quintiles

DPPS through SBP reduction						
Overall						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	4812	806	941	996	1014	1054
95% LL	2011	265	320	390	463	540
95% UL	7625	1356	1573	1598	1557	1549
Population wide changes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	4106	659	745	850	898	954
95% LL	1416	138	168	269	365	456
95% UL	6713	1165	1304	1414	1419	1442
Anti-hypertension treatment						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	705	147	196	146	116	100
95% LL	198	45	46	39	31	30
95% UL	1808	370	528	386	312	247

Table Q: CHD deaths prevented or postponed through medication and population changes in SBP between 2000 and 2007 in England, stratified by deprivation quintiles

DPPS through Cholesterol reduction						
Overall						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	4078	709	836	875	829	829
95% LL	2150	400	365	371	414	498
95% UL	8149	1246	1905	2242	1681	1407
Population wide changes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	1766	381	270	271	349	495
95% LL	916	234	99	88	175	311
95% UL	2615	535	442	450	521	675
Statins treatment						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	2312	327	566	605	480	334
95% LL	684	85	155	159	130	83
95% UL	6184	861	1648	1992	1351	912

Table R: CHD deaths prevented or postponed through medication and population changes in cholesterol between 2000 and 2007 in England, stratified by deprivation quintiles

5.2. Women

DPPS through changes in the population						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	7380	1053	1652	1487	1495	1694
95% LL	3673	341	834	682	730	1062
95% UL	10669	1679	2370	2197	2175	2264
DPPS through changes in the treatments uptakes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	4081	937	623	962	944	615
95% LL	1692	342	261	383	365	246
95% UL	8916	2402	1357	2250	2112	1494

Table S: CHD deaths prevented or postponed through medication and population changes in SBP and Cholesterol between 2000 and 2007 in England, stratified by deprivation quintiles

DPPS through SBP reduction						
Overall						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	8149	1412	1638	1733	1722	1644
95% LL	4422	696	822	917	955	1011
95% UL	11540	2064	2366	2475	2420	2218
Population wide changes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	7056	1202	1424	1471	1492	1467
95% LL	3446	513	628	701	745	854
95% UL	10329	1816	2136	2176	2161	2018
Anti-hypertension treatment						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	1093	210	215	262	229	177
95% LL	319	63	64	75	65	53
95% UL	2624	510	520	641	575	433

Table T: CHD deaths prevented or postponed through medication and population changes in SBP between 2000 and 2007 in England, stratified by deprivation quintiles

DPPS through Cholesterol reduction						
Overall						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	3313	577	637	717	717	665
95% LL	1069	18	298	179	171	304
95% UL	8202	2065	1335	2005	1904	1562
Population wide changes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	325	-149	228	16	2	227
95% LL	-315	-264	99	-123	-134	97
95% UL	996	-31	364	161	144	365
Statins treatment						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	2988	727	409	700	714	438
95% LL	922	190	115	197	199	123
95% UL	7822	2203	1095	2009	1905	1323

Table U: CHD deaths prevented or postponed through medication and population changes in cholesterol between 2000 and 2007 in England, stratified by deprivation quintiles

5.3. Percentage difference in men relative to women

DPPS through changes in the population						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	13%	-17%	33%	16%	8%	11%
95% LL	-74%	-222%	-35%	-80%	-87%	-49%

95% UL	61%	58%	75%	67%	58%	49%
DPPS through changes in the treatments uptakes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	15%	40%	-43%	6%	26%	19%
95% LL	-101%	-49%	-262%	-165%	-91%	-105%
95% UL	74%	85%	56%	76%	80%	79%

Table V: Percentage difference of DPPs for men relative to women through medication and population changes in SBP and Cholesterol between 2000 and 2007 in England

DPPS through SBP reduction						
Overall						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	36%	37%	40%	38%	37%	33%
95% LL	-24%	-32%	-33%	-25%	-20%	-19%
95% UL	75%	80%	79%	77%	74%	68%
Population wide changes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	34%	36%	44%	37%	34%	31%
95% LL	-38%	-47%	-37%	-41%	-37%	-29%
95% UL	80%	89%	88%	81%	76%	70%
Anti-hypertension treatment						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	19%	17%	-15%	29%	35%	32%
95% LL	-128%	-145%	-243%	-103%	-90%	-96%
95% UL	81%	79%	77%	85%	87%	84%

Table W: Percentage difference of DPPs for men relative to women through medication and population changes in SBP between 2000 and 2007 in England

DPPS through Cholesterol reduction						
Overall						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	-52%	-458%	-48%	-69%	-57%	-40%
95% LL	-273%	-1102%	-246%	-448%	-367%	-180%
95% UL	53%	78%	49%	61%	61%	48%
Population wide changes						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	-25%	402%	-35%	1065%	680%	-148%
95% LL	-6102%	215%	-211%	-6121%	-7144%	-436%
95% UL	6040%	1190%	59%	5990%	6646%	-15%
Statins treatment						
	England	**IMD quintile 1**	**IMD quintile 2**	**IMD quintile 3**	**IMD quintile 4**	**IMD quintile 5**
		Affluent				**Deprived**
Mean	5%	42%	-80%	-15%	14%	4%
95% LL	-173%	-84%	-465%	-288%	-160%	-184%
95% UL	79%	91%	65%	79%	84%	84%

Table X: Percentage difference of DPPs for men relative to women through medication and population changes in cholesterol between 2000 and 2007 in England

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STROBE statement checklist of items that should be included in reports of observational studies

The contribution of primary prevention medication and dietary change in coronary mortality reduction in England between 2000 and 2007: a modelling study

Maria Guzman Castillo et al.

	Item No	Recommendation	
		Title and abstract	
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	No
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract attached (page 2)
		Introduction	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background & rationale explained page 5
Objectives	3	State specific objectives, including any pre-specified hypotheses	Specific objective stated in page 5
		Methods	
Study design	4	Present key elements of study design early in the paper	Key elements presented Pages 6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Data collection specified and fully detailed in the technical appendix and pages 6-7
Participants	6	(*a*) *Cohort study*? Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*? Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	NA
		Cross sectional study? Give the eligibility criteria, and the sources and methods of selection of participants	**Cross sectional study.** eligibility criteria, sources and methods of selection of cases clearly specified in the technical appendix and methods (page 6-7)
		(*b*) *Cohort study*? For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*? For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers.	Outcomes, exposures, predictors, potential confounders, and effect modifiers clearly described. Pag 6-

	Item No	Recommendation	
		Give diagnostic criteria, if applicable	Pages 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Diagnostic criteria based on ICD codes.
Bias	9	Describe any efforts to address potential sources of bias	Age adjustment and stratification by socio-economic circumstances detailed. Pages 6-7
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods described in detail Pages 6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical methods described in detail Pages 6-7 and Technical appendix
		(*b*) Describe any methods used to examine subgroups and interactions	Subgroup analyses detailed Pages 6-7 and Technical appendix
		(*c*) Explain how missing data were addressed	Details on how missing data were addressed are included. Technical appendix
		(*d*) *Cohort study*? If applicable, explain how loss to follow-up was addressed *Case-control study*? If applicable, explain how matching of cases and controls was addressed *Cross sectional study*?If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	Sensitivity analysis implemented and described Pages 6-7 and Technical appendix
		Results	
Participants	13*	(*a*) Report numbers of individuals at each stage of study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Reported Pages 8--16 and technical appendix
		(*b*) Give reasons for non-participation at each stage	NA
		(*c*) Consider use of a flow diagram	NA
Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Details provided Reported Pages 8-16 and technical appendix
		(*b*) Indicate number of participants	NA

	Item No	Recommendation	
		with missing data for each variable of interest	
		(*c*) *Cohort study*? Summarise follow-up time (eg average and total amount)	NA
		Cohort study? Report numbers of outcome events or summary measures over time	NA
Outcome data	15*	*Case-control study?* Report numbers in each exposure category, or summary measures of exposure	NA
		Cross sectional study? Report numbers of outcome events or summary measures	Events detailed Reported Pages 14-16
Main results	16	(*a*) Report the numbers of individuals at each stage of the study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Numbers detailed
		(*b*) Give reasons for non-participation at each stage	NA
		(*c*) Consider use of a flow diagram	NA
Other analyses	17	Report other analyses done? eg analyses of subgroups and interactions, and sensitivity analyses	Sub-group analyses and comparisons detailed Sensitivity analysis implemented and described Reported Pages 8-16 and technical appendix
		Discussion	
Key results	18	Summarise key results with reference to study objectives	Key results summarised. Reflect objectives.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations and potential biases discussed in detail page 14 and15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Cautious throughout. Pages 8-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	Generalisability briefly discussed. Pages 8-16
		Other information	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding sources detailed Page 17